ATTACHMENT D

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PROPOSED RULES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 334

(Docket No. 78N-036L)

RIN 0905-AA06

Laxative Drug Products For Over-The-Counter Human Use; Proposed Amendment to The Tentative Final Monograph

Thursday, September 2, 1993

***46589** AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking to amend the tentative final monograph for over-the-counter (OTC) laxative drug products to include conditions under which docusate salts, i.e., docusate calcium, docusate potassium, and docusate sodium, are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products (the Panel), public comments on the advance notice of proposed rulemaking that was based on those recommendations, and a comment submitted in response to the tentative final monograph for OTC laxative drug products that was published in the Federal Register of January 15, 1985 (50 FR 2124). This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by December 31, 1993. New data by September 2, 1994. Comments on the new data by November 2, 1994. Written comments on the agency's economic impact determination by December 31, 1993.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

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SUPPLEMENTARY INFORMATION: In the Federal Register of March 21, 1975 (40 FR 12902), FDA published, under §330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Panel, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. The agency's proposed regulation, in the form of a tentative final monograph, for OTC laxative drug products was published in the Federal Register of January 15, 1985 (50 FR 2124).

In the advance notice of proposed rulemaking, the Panel recommended that docusate calcium [FN1], docusate potassium [FN2], and docusate sodium [FN3] in the recommended dosages be classified in Category I (generally recognized as safe and effective) as OTC stool softener laxatives (40 FR 12902 at 12912). Subsequently, FDA became aware of information in animal studies implicating docusate sodium as a potential animal teratogen (Refs. 1, 2, and 3), thereby raising questions about the Panel's conclusions and recommendations for these laxative ingredients. Because evaluation of the animal studies had not been completed when FDA published the tentative final monograph on OTC laxative drug products in 1985, the agency did not discuss docusate salts and stated that a separate document would be published to address the status of these ingredients (50 FR 2124 at 2125). The agency has completed its evaluation of these animal studies and is now proposing that these docusate salts are safe and effective for OTC laxative use.

FN1 The Panel designated this ingredient "dioctyl calcium sulfosuccinate." However, docusate calcium is currently the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1992."

FN2 The Panel designated this ingredient "dioctyl potassium sulfosuccinate." However, docusate potassium is currently the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1992."

FN3 The Panel designated this ingredient "dioctyl sodium sulfosuccinate." However, docusate sodium is currently the official name for this ingredient in the "USAN and the USP dictionary of drug names, 1992."

In response to the advance notice of proposed rulemaking, seven manufacturers, one university, and one individual submitted comments concerning docusate salts. These comments are also addressed in this document. Copies of the comments received are on public display in the Dockets Management Branch (address above).

The chemical name for docusate sodium is butanedioic acid, sulfo-, 1,4-bis(2-ethylhexyl)ester, sodium salt (Ref. 4). Docusate calcium, docusate potassium, and docusate sodium are chemically identical, with the exception of the substitution of a calcium or potassium salt for the sodium salt. The agency is unaware of any data demonstrating that the substitution of the calcium or potassium ion for the sodium ion in the docusate formulation would have a significant effect on the biological activity of the docusate anion. The agency believes that any toxicological effects are due to the organic portion of the molecule, and not to the calcium, potassium, or sodium portion.

Oral administration of docusate calcium and docusate sodium has been studied in pregnant rats (Ref. 1). Ingestion of docusate calcium at levels of 1,500 to 2,000 milligrams per kilogram (mg/kg) body weight or docusate sodium at levels of 2,000 mg/kg by pregnant rats throughout gestation days 6 through 15 resulted in increased fetal resorptions and produced significant incidences of fetal malformations, consisting primarily of exencephaly frequently associated with spina bifida and microphthalmia. However, 2,000 mg/kg of docusate calcium was not teratogenic when ingested for shorter periods of time (days 6 to 8, 8 to 10, or 10 to 12) during gestation.

In the same study, gavage dosing of docusate calcium at 750 mg/kg per day (mg/kg/day) during days 6 to 15 of gestation resulted in fetal resorptions and skeletal abnormalities, primarily incomplete ossification of cranial bones. In most instances, mean maternal weight gain was somewhat reduced after gavage doses of 750 mg/kg. Docusate calcium administered by gavage to pregnant rats at 1,000 and 1,500 mg/kg during various 3-day periods of gestation was not teratogenic but did cause fetal resorption and maternal deaths. The data from these teratology studies in the rat support a no-effect level of 500 mg/kg of docusate calcium, which is 100 times the human laxative dose of 300 mg/day.

***46590** A teratology study of docusate calcium in dogs was inconclusive (Ref. 2). Pregnant dogs received 0, 50, or 200 mg/kg of docusate calcium in capsules during gestational days 14 through 30. Fetuses were surgically delivered on the 55th day of gestation and examined for gross external, internal soft tissue, and skeletal malformations. There were some minor fetal skeletal malformations in the 50 mg/kg group. However, because of the lack of good controls, it could not be determined whether these were embryotoxic effects of docusate calcium or reflected normal skeletal variations in this strain. The toxic effects in the 200 mg/kg treated group included resorptions, fetal weight loss, and malformations. However, at this dose, it was not possible to distinguish the teratogenic effects of the docusate calcium from the effects of general maternal toxicity.

A three-generation reproduction dietary exposure study of docusate sodium at levels of 0, 0.5, and 1 percent in the diet was conducted in rats (Ref. 3). Mothers received 0.5 percent (approximately 440 mg/kg/day) or 1 percent (approximately 890 mg/kg/day) of docusate sodium prior to the first mating. Successive generations were divided into two groups: (1) Mothers who were fed docusate sodium continuously, and (2) mothers who stopped receiving docusate sodium 24 hours prior to expected delivery and did not receive any throughout lactation. Pups from group one mothers exhibited decreased mean body weight and increased mortality prior to weaning compared to pups from group two mothers. No malformations were noted among any of the pups. However, because it was not reported whether the births were supervised, it was not possible to rule out the possibility that the mothers ate any deformed pups. No maternal toxicity from docusate sodium was noted. The agency was unable to assign a no-effect level for docusate sodium in this study because preweaning deaths occurred at the lowest dose level tested. The design of the study was inadequate to determine whether docusate sodium was directly or indirectly toxic to pups because the docusate may have altered the taste of the milk, which the pups then refused to drink, or because the mothers were not secreting milk.

The possibility exists in these rat studies that docusate sodium produced teratogenic and reproductive effects in rats by interfering with pantothenic acid by blocking its absorption or perhaps its utilization. Pantothenic acid deficiency in pregnant rats has been associated with resorptions and malformations, most frequently exencephaly and eye malformations. These fetal effects can occur in the absence of obvious signs of toxicity in pregnant rats. A possible mechanism by which docusate calcium and docusate sodium create a deficiency of pantothenic acid has been ascribed to micellar entrapment of pantothenate in the small intestine by high levels of docusate. One unresolved matter, however, was that concentrations of pantothenic acid were not determined in maternal liver or in the fetus, so it was not known if a general deficiency state was created or if the docusate interfered with the cellular activities of pantothenic acid in the fetus.

FDA considered the above data as suggesting that docusate salts were teratogenic in animals, thereby suggestive of possible human effects. Therefore, FDA convened a panel of scientists from other agencies within the Federal government to review the available data, information, and views concerning the teratogenicity and reproductive toxicity of docusate salts. The Dioctyl Sodium Sulfosuccinate Scientific Review Panel (the DSS Panel) issued its report in March 1984 (Ref. 5) with the following conclusions:

(1) Docusate calcium, docusate potassium, and docusate sodium should not be considered potential human teratogens.

(2) The findings of the three-generation reproduction study of docusate sodium in rats (in which treatment was continued through lactation and a significant decrease in pup survival was observed during lactation) provide grounds for concern that should be explored further.

(3) There was no compelling reason to alter the accepted 1,000-fold safety factor (used for teratogens by FDA) based on the data reviewed.

(4) For therapeutic uses of docusate sodium, a safety margin of nearly 120-fold is adequate.

(5) The data suggest that docusate sodium has the potential to produce adverse reproductive effects in the laboratory animals treated with large doses, but it appears the human risk is very low.

The DSS Panel, therefore, recommended conduct of the following studies:

(1) A standard FDA three-generation reproductive study of docusate sodium using rats and mice and including pair-fed and untreated controls.

(2) Additional pharmacokinetics and biotransformation studies of docusate sodium to include a determination of the occurrence of docusate sodium and its metabolites in breast milk.

(3) Continued epidemiologic surveillance of pregnancy outcome in women treated with docusate salts.

Subsequently, FDA amended its proposed requirements to:

(1) Defer the reproduction study in mice, pending completion and evaluation of the reproduction study in rats, (2) delete the pair-fed controls in the reproduction study, and (3) require performance of a pharmacokinetic study if toxic effects in rat pups during lactation were confirmed.

A final report of the rat reproduction study was submitted to the agency as a citizen petition to reopen the administrative record for this rulemaking (Ref.

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6. In this study, docusate sodium was administered in the diet to three successive generations of male and female rats with 30 rats per sex per group (30/sex/group) at levels of 0.0, 0.1, 0.5, and 1 percent. The males in the original parental group (F0) were exposed to the diets for at least 10 weeks and the females were exposed for 2 weeks prior to mating that produced the F1 litters. All descendant animals were exposed to the test material in utero, while nursing, continuously from weaning throughout mating, gestation, and lactation. The exceptions were the F3 litters that were sacrificed after weaning and animals from other generations that were culled or not selected for parents of the succeeding generation. The report included summaries and individual data on mean body weight, body weight gain, food consumption, and compound consumption for males and females during the premating phases; group mean and individual body weight and food intake data and compound consumption for females during gestation and lactation; male fertility indices, summary and individual litter data through day 21 of lactation, and gross pathological observations of all adults and the F3 weanlings.

After reviewing these data, the agency concluded that docusate sodium administered in the diet to three successive generations of rats at levels of 0.5 percent and 1 percent caused a reduction in body weights for parental males of all generations and for F1 and F2 females. In addition, the pup weights were lower than those of the controls. There was no evidence of effects on growth or reproductive performance except for the isolated incidence of an increased number of pups born dead (stillbirths) in the F3 litters of the 1 percent group, and some pups in the F2 and F3 litters had suckling problems.

The high percentage (90 percent or greater) of pup survival to weaning in this study might be attributed to the ***46591** high quality of the conduct of the study and the analysis of the diet for pantothenic acid content to ensure that the level of the vitamin was optimal. After further evaluation, the agency concluded that the teratogenicity seen in earlier studies of docusate calcium and docusate sodium in this species (Ref. 3) was due specifically to a surfactant induced deficiency of the B vitamin calcium pantothenate.

To address the question of human risk involving use of docusate sodium and a possible pantothenic acid deficiency, the agency examined the literature to determine if there was any evidence of this problem. The agency was unable to find any clinical evidence in the literature that showed pantothenic acid deficiency or possible toxicity problems, even to a moderate degree. The distribution of pantothenic acid in foods is so widespread that an occurrence of a deficiency of the vitamin is probably extremely rare (Refs. 7 and 8). In fact, evidence of dietary deficiency of pantothenic acid alone has not been clinically recognized in man. A deficiency syndrome has been experimentally induced in human volunteers by administration of a metabolic antagonist, omega-methylpantothenic acid, imposed on a pantothenic acid-deficient diet. However, it has been impossible to induce an isolated deficiency of the vitamin in less than at least 9 months on a natural diet alone (Ref. 8). The customary intake of pantothenic acid from ordinary foods in the United States is approximately 5 to 20 mg/day (Ref. 8). The estimated safe and adequate daily dietary intake of pantothenic acid for adults is estimated to be 5 to 10 mg/day (Ref. 8). Therefore, the probability of observing pantothenic acid deficiency in the

United States is considered to be extremely low.

A search of the literature from 1985 through 1991 has revealed no articles suggesting teratogenic or reproductive problems associated with docusate salts. Results of epidemiologic surveillance of pregnancy outcome in women treated with docusates have been inconclusive, supporting neither safety nor increased risk of birth defects (Ref. 9).

The usual daily human dose of docusate sodium as a laxative is 50 to 500 mg/day (Ref. 10), which is 1 to 10 mg/kg/day based on the FDA standard of an average adult weight of 50 kg. The no adverse effect level from teratology studies in rats is 500 mg/kg/day; for reproductive toxicity it is about 50 to 150 mg/kg/day. After considering these data, the agency has determined that the human dosages of docusate salts proposed in this tentative final monograph do not pose reproductive or teratological problems and that these ingredients can be generally recognized as safe and effective OTC laxatives. The agency is amending §334.20 to include docusate salts as stool softener laxatives. In addition to the specific labeling proposed for these ingredients in §334.62 in this document, docusate salts will also be required to bear the labeling proposed for all laxative drug products in §334.50 (50 FR 2124 at 2153). Section 334.50 limits use of the product to "relief of occasional constipation" and proposes the following warnings: (1) "Do not use laxative products when abdominal pain, nausea, or vomiting are present unless directed by a doctor," (2) "If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a doctor before using a laxative," (3) "Laxative products should not be used for a period longer than 1 week unless directed by a doctor," (4) "Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition. Discontinue use and consult your doctor," (5) "Do not use this product if you are on a low salt diet unless directed by a doctor" for products containing more than 5 milliequivalents (115 mg) of sodium in the maximum recommended daily dose, and (6) "Do not use this product if you have kidney disease unless directed by a doctor" for products containing more than 25 milliequivalents (975 mg) of potassium in the maximum recommended daily dose. (In the Federal Register of April 25, 1991 (56 FR 19222), the agency proposed to amend the general labeling provisions for OTC drug products to provide uniform sodium content labeling for all orally administered OTC drug products. Should that proposed amendment be published as a final rule, any existing requirements relating to sodium labeling in the laxative monograph will be superseded.) The agency believes that the proposed labeling will provide for the safe and effective OTC use of docusate salts. Accordingly, in this amendment to the tentative final monograph for OTC laxative drug products, the agency is proposing that docusate calcium (oral dosage forms), docusate potassium (rectal enema dosage form), and docusate sodium (oral dosage forms) be classified as Category I stool-softener laxative ingredients at the dosages discussed below.

References

(1) Hoechst-Roussel Pharmaceuticals,Inc., "Teratogenic Evaluation of Larger Oral Dosages of Dioctyl Calcium Sulfosuccinate (and Dioctyl Sodium

Sulfosuccinate) in the Rat," Experiment 0972-45, OTC Vol. 090043, Docket No. 78N-036L, Dockets Management Branch.

(2) International Research and Development Corp. for Hoechst-Roussel Pharmaceuticals, Inc., "DCS Teratology Study in Beagle Dogs," in the final report of the Dioctyl Sodium Sulfosuccinate Scientific Review Panel, app. 4, Attachment 62, March 1984, Docket No. 84N-0184, Dockets Management Branch.

(3) American Cyanamid Co., "Aerosol OT: Successive Generation Studies in Rats," Report No. 70-239, OTC Vol. 090093, Docket No. 78N-036L, Dockets Management Branch.

(4) "USAN and the USP Dictionary of Drug Names," edited by C. A. Fleeger, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 220, 1992.

(5) Final Report of the Dioctyl Sodium Sulfosuccinate Scientific Review Panel, "Reproductive Toxicity of Dioctyl Sodium and Calcium Sulfosuccinate--A Report to the Acting Commissioner of Food and Drugs,"March 1984, Docket No. 84N-0184, Dockets Management Branch.

(6) Comment No. CP6, Docket No. 78N-036L, Dockets Management Branch.

(7) Shils, M. E., and V. R. Young, "Modern Nutrition in Health and Disease," 7th ed., Lea & Febiger, Philadelphia, pp. 383-387, 1988.

(8) Gennaro, A., editor, "Remington's Pharmaceutical Sciences," 18th ed., Mack Publishing Co., Easton, PA, pp. 1016-1017, 1990.

(9) Rosa, F. W., "Birth Defect Diagnoses with First Trimester Docusate Exposures in Michigan Medicaid Data," draft of unpublished study, dated June 2, 1987, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

(10) "USP DI, Drug Information for the Health Care Professional," Vol. I, 13th ed., United States Pharmacopeial Convention, Inc., Washington, pp. 1717-1759, 1993.

I. The Agency's Tentative Conclusions on The Comments

1. One comment requested that the Panel's recommendation in §334.20(c), which provides for an oral dosage form of docusate sodium, be amended to provide for a rectal dosage form of this ingredient. The comment argued that the Panel provided for a rectal dosage form of docusate potassium in §334.20(b) and concluded that the calcium, potassium, and sodium docusate salts are safe and effective in the amounts usually taken orally or rectally in laxative drug products (40 FR 12902 at 12912). The comment concluded that the monograph should provide for the same rectal dosage of docusate sodium in §334.20(c) as present for docusate potassium in §334.20(b).

The agency has reviewed the Panel's recommendations regarding oral and rectal dosage forms of docusate salts (40 FR 12902 at 12941). The Panel recommended as Category I an oral ***46592** dosage for docusate calcium and docusate sodium of 50 to 360 mg daily for adults and children over 12 years of age. For docusate calcium, the Panel recommended an oral dosage of 50 to 150 mg daily for children 2 to 12 years of age, and 25 mg daily for infants under 2 years of age. For docusate sodium, the recommended dosage was 50 to 150 mg daily for children 2 to 12 years of age, and 20 to 25 mg for infants under 2 years of age. The Panel also recommended as Category I a rectal dosage of docusate potassium of 50 to 250 mg daily for adults and children over 12 years of age, and 100 mg daily for

children 2 to 12 years of age.

As discussed above, docusate calcium, docusate potassium, and docusate sodium are chemically identical, with the exception of the substitution of a calcium or potassium salt for the sodium salt. The data on the marketed products submitted to the Panel included information only on oral dosage forms for docusate calcium and docusate sodium, and on rectal enema dosage forms for docusate potassium. The agency is unaware of any data demonstrating that the substitution of the calcium or potassium ion for the sodium ion in the docusate formulation would have a significant effect on the biological activity of the docusate anion. The agency is aware of several products in which docusate potassium is marketed in an oral dosage form (Refs. 1 and 2) and no products in which docusate calcium is marketed in a rectal dosage form (Refs. 2 and 3). Although the American Drug Index lists three products in which docusate sodium is marketed in a rectal dosage form (Ref. 3), the manufacturers of these products state that the products are not currently marketed (Refs. 4, 5, and 6). No safety or effectiveness data have been submitted for any of these products and, in addition, no data have been submitted to show that the individual docusate salts are therapeutically equivalent when used interchangeably in oral or rectal dosage forms. Thus, the agency concludes that safety and effectiveness have been established only for the docusate salt dosage forms recommended by the Panel, and these are the only dosage forms being included in this tentative final monograph. Manufacturers of docusate salt products in other dosage forms, as noted above, need to submit data on these products to support the use of the various docusate salts interchangeably in both oral and rectal dosage forms. Such data should address the safety of the docusate salt in the dosage form not included in the monograph and the pharmacologic/therapeutic equivalence of the specific docusate salt(s) in both oral and rectal dosage forms. The agency invites interested persons to submit such data for consideration.

References

(1) "Physicians' Desk Reference forNonprescription Drugs," 14th ed., Medical Economics Data, Montvale, NJ, pp. 668-669, 1993.

(2) Curry, C. E., and D. Tatum-Butler, "Laxative Products" in "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, pp. 343-378, 1990.

(3) Billups, N. F., and S. M. Billups, editors, "American Drug Index," 36th ed., J. B. Lippincott Co., St. Louis, pp. 204-205,1991.

(4) Memorandum of telephone conversation between L. Gilbert, WebconPharmaceuticals, and D. Hernanedz, FDA, dated September 14, 1992, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

(5) Memorandum of telephone conversation between S. Kolakowsky, Carter Products, and D. Hernandez, FDA, dated September 14, 1992, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

(6) Memorandum of telephone conversation between S. Scheindlin, Lemmon Co., and D. Hernandez, FDA, dated September 14, 1992, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

2. Several comments objected to the wording of the drug interaction precaution

recommended by the Panel in §334.62(b), which states: "Do not take this product if you are presently taking a prescription drug or mineral oil." One comment argued that this drug interaction precaution was unnecessarily discriminatory and should be deleted because many food products that are consumed daily contain natural and synthetic emulsifiers, surfactants, and "softening agents" that may cause interactions with oral prescription drugs or mineral oil. Two of the comments argued that unless specific adverse drug interactions can be proven, it is not appropriate to require a general precaution statement. Another comment argued that it would be more useful to the consumer if known specific drugs, such as mineral oil, that interact with stool softeners were listed rather than using a general warning against the use of stool softeners with prescription drugs. Three of the comments urged that the drug interaction precaution in § 334.62(b) be further amended to add the statement "* * * except on the advice of a physician," because doctors often recommend the concomitant use of a laxative product to counteract the constipation problem that may occur with some prescription drugs. One comment further suggested that the negatively worded drug interaction precaution be revised to read, "Consult your physician if you are taking mineral oil," because this positively worded statement would help consumers avoid the chance of a drug interaction.

The agency does not consider the drug interaction precaution statement in § 334.62(b) to be discriminatory because the laxative monograph sets forth conditions for the safe and effective use of ingredients for drug and not food use. Although foods may contain surfactants such as those found in stool softener laxatives, these ingredients are generally present in foods in much lower amounts than in laxatives and, therefore, pose a much lower risk of interaction with drugs.

The Panel suggested a possible interaction between the stool softener ingredients and prescription drugs significant enough to justify a warning and stated that docusate sodium possesses potent detergent properties that may facilitate gastrointestinal or hepatic uptake of other drugs, thereby potentiating their activities (40 FR 12902 at 12912). The agency, however, has been unable to verify that any detrimental interaction occurs. A search of scientific literature reveals no conclusive data or information to substantiate this suggested problem (Refs. 1 through 7). One pilot bioavailability study (Ref. 7) suggested that there is a reduction in tetracycline availability due to docusate sodium, but the results were not statistically significant in this small study. The agency invites any interested person to submit data showing an interaction between docusate salts and any prescription drug for the agency's consideration.

The agency agrees with the Panel that the absorption of mineral oil may be enhanced by docusate sodium and these agents should not be taken concurrently (40 FR 12902 at 12912).

The agency disagrees with the suggestion that the negatively worded drug interaction precaution "Do not take this product if * * *" would be more helpful to consumers if reworded to read, "Consult your physician if * * *," because the key advice is that consumers should not take the drug under certain circumstances. The wording suggested by the comment could easily mislead consumers into thinking that they should take the product first and consult

their physician later. The agency agrees, however, that the drug interaction precaution should be expanded to allow concomitant use of stool softeners with mineral oil if ***46593*** deemed necessary by a doctor. In an effort to make the labeling clearer and easier to understand, the phrase suggested by several comments "* * * except on the advice of a physician" has been simplified and reworded to "* * * unless directed by a doctor." Accordingly, in this tentative final monograph, this drug interaction precaution is revised to read: "Drug interaction precaution: Do not take this product if you are presently taking mineral oil, unless directed by a doctor."

References

(1) Brunton, L. L., "Agents AffectingGastrointestinal Water Flux and Motility, Digestants, and Bile Acids" in "The Pharmacological Basis of Therapeutics, 8th ed., edited by A. G. Gilman, et al., Pergamon Press Co., Inc., New York, pp. 914-932, 1990.

(2) Osol, A., R. Pratt, and A. Gennaro,"The United States Dispensatory," 27th ed., J. B. Lippincott Co., Philadelphia, pp. 438-439, 1973.

(3) Curry, C. E., and D. Tatum-Butler, "Laxative Products" in "Handbook of Nonprescription Drugs," 9th ed., American Pharmaceutical Association, Washington, pp. 343-378, 1990.

(4) "USP DI, Drug Information for the Health Care Professional," Vol. I, 13th ed., United States Pharmacopeial Convention, Inc., Washington, pp. 1717-1759, 1993.

(5) "Drug Evaluations," 6th ed.,American Medical Association, Chicago, p. 982, 1986.

(6) Gennaro, A., editor, "Remington'sPharmaceutical Sciences," 18th ed., Mack Publishing Co., Easton, PA, pp. 1016-1017, 1990.

(7) Shah, V. P., et al., "Influence of Dioctyl Sodium Sulfosuccinate on the Absorption of Tetracycline," Biopharmaceutics and Drug Disposition, 7:27-33, 1986.

3. One comment expressed concern about the Panel's Category I classification of docusate sodium in combination with stimulant laxatives in §334.32(a), which included as oral dosage forms: (1) Docusate sodium and casanthranol, (2) docusate sodium and danthron, (3) docusate sodium and phenolphthalein, (4) docusate sodium and senna concentrate, and (5) docusate calcium and danthron. The comment cited three references that discuss the potential dangers of such combinations (Refs. 1, 2, and 3). The comment felt that the Panel's report was well-researched, but expressed surprise that these references were not mentioned.

The agency has reviewed the references cited by the comment and notes that they were not reviewed by the Panel. The article by Smith (Ref. 1) deals with possible damage to the myenteric plexus from long-term administration of anthraquinone laxatives and does not address any problems or dangers arising from the administration of combinations of docusate sodium and stimulant laxatives. The other two references (Refs. 2 and 3) both quote the same study in which the oral LD50 for danthron (1,8-dihydroxyanthraquinone) in rats was lowered from over 22 mg/kg when administered alone to 9 mg/kg when administered

in combination with an unspecified amount of docusate sodium. The study concludes that this effect can only be due to increased absorption of danthron because the animals died with symptoms of systemic toxicity.

A well-designed, well-controlled study by Case, Smith, and Nelson (Ref. 4) in mice shows considerably higher LD50 values of 7 grams per kilogram (g/kg) for danthron, 2.64 g/kg for docusate sodium, and 3.42 g/kg for a danthron/docusate sodium mixture (1:2 ratio). This study attributes the lower LD50 values cited in the two earlier studies (Refs. 2 and 3) to a typographical error in the original study. Case, Smith, and Nelson point out that the mg/kg values are more logical and in closer agreement with current findings if read in terms of g/kg rather than mg/kg. Case, Smith, and Nelson also conducted a 1-year chronic toxicity study in dogs (Ref. 4). No toxic effects and no evidence of any changes in the myenteric plexus at levels of 15 mg/kg/day of danthron in combination with 30 mg/kg/day of docusate sodium were shown. Because these levels are considerably lower than the g/kg amounts discussed above, the agency concludes that the comment's concerns have been adequately addressed by subsequent reports in the literature.

In January 1987, a leading U. S. pharmaceutical manufacturer informed FDA that it would voluntarily cease manufacture and distribution of products containing danthron. The company's decision was partly in response to published studies in Britain and Japan that strongly suggested that chronic administration of high doses of danthron to rats and mice resulted in the development of intestinal and liver tumors and that danthron is, therefore, potentially a carcinogen in man (Refs. 5 and 6). Danthron, in common with other anthraquinone compounds, has also been shown to exhibit a positive mutagenic effect in some in vitro models (Refs. 7 and 8). FDA subsequently initiated a total recall to the retail-dispensing level of all danthron-containing drug products, by sending a recall letter to all registered drug firms and distributors (Ref. 9). FDA stated that "danthron toxicity in humans has not been specifically demonstrated, but because of potential risk, FDA has requested an immediate halt to all manufacturing, relabeling, repackaging, and further distribution of human drug products containing danthron" (Ref. 10). Accordingly, FDA is not including the combination of docusate sodium and danthron in this tentative final monograph. The other four docusate salt and stimulant laxative combination products mentioned by the comment and recommended as Category I by the Panel are being proposed for inclusion in the monograph in the absence of specific data indicating a safety problem.

References

(1) Smith, B., "Effect of Irritant Purgatives on the Myenteric Plexus in Man and the Mouse," Gut, 9:139-143, 1968.

(2) Smith, B., "The Neuropathology of the Alimentary Tract," The Williams and Wilkins Co., Baltimore, pp. 92-98, 1972.

(3) Godfrey, H., "Dangers of Dioctyl Sodium Sulfosuccinate in Mixtures," Journal of the American Medical Association, 215:643, 1971.

(4) Case, M. T., J. K. Smith, and R. A. Nelson, "Acute Mouse and Chronic Dog Toxicity Studies on Danthron, Dioctyl Sodium Sulfosuccinate, Paloxalkol and

Combinations,"Drug and Chemical Toxicology, 1:89-101, 1977.

(5) Mori, H., et al., "Induction ofIntestinal Tumors in Rats by Chrysazin," British Journal of Cancer, 52:781-783, 1985.

(6) Mori, H., et al., "Carcinogenicity of Chrysazin in Large Intestine and Liver of Mice," Japanese Journal of Cancer Research, 77:871-876, 1986.

(7) Brown, J. P., and R. J. Brown, "Mutagenesis by 9,10-Anthraquinone Derivatives and Related Compounds in Salmonella Typhimurium," Mutation Research, 40:203-224, 1976.

(8) Tikkanen, L., T. Matsushima, and S. Natori, "Mutagenicity of Anthraquinones in the Salmonella Preincubation Test," Mutation Research, 116:297-303, 1983.

(9) FDA drug recall letter concerningdanthron-containing drug products, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

(10) FDA press release on danthron drug products, in OTC Vol. 090TFM2, Docket No. 78N-036L, Dockets Management Branch.

4. One comment requested that recommended §334.32(b)(1) be amended to provide for a combination of docusate sodium and glycerin in a rectal dosage form, in addition to the combination of docusate potassium and glycerin recommended by the Panel. The comment argued that historically docusate sodium is the best-known and most widely used of the docusate salts, that it is pharmaceutically compatible with glycerin, and that it is no less effective and no more toxic than docusate potassium.

The agency is unaware of any data demonstrating that the substitution of the sodium ion for the potassium ion in ***46594** the docusate formulation would have a significant effect on the biologic activity of the docusate anion (see comment 1). However, no data have been submitted to support the assumption that the effectiveness of docusate sodium would be comparable to docusate potassium in a combination rectal dosage formulation with glycerin or that the toxicity would not be increased. Therefore, the agency is not including in this tentative final monograph the rectal dosage form combination recommended by the comment. The agency is including in this tentative final monograph the two rectal enema dosage combinations classified by the Panel as Category I: (1) Docusate potassium and glycerin, and (2) docusate potassium and sorbitol.

II. The Agency's Tentative Conclusions and Adoptionof The Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and III Conditions

1. Summary of Ingredient Categories

The agency has reviewed the docusate salt active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's Category I classification of docusate calcium and docusate sodium in oral dosage forms and docusate potassium in a rectal dosage form for use as OTC laxative drug products. As a convenience to the reader, the following list is included as a summary of the Panel's recommendations and the agency's proposed categorization of stool softener active ingredients.

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(Cite as: 58 FR 46589, *46594)

Active ingredient	Panel	Agency
Docusate calcium	I	I
Docusate potassium	I	I
Docusate sodium	I	I

2. Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any docusate salt condition not included in this tentative final monograph by following the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph conditions for docusate salt ingredients with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The wording of the drug interaction precaution recommended by the Panel in §334.62(b) has been revised to read: "Drug interaction precaution: Do not take this product if you are presently taking mineral oil, unless directed by a doctor." (See comment 2.)

2. The agency is not including in this tentative final monograph the combinations of docusate calcium or docusate sodium and danthron because of a 1987 recall of all danthron-containing products based on evidence of potential carcinogenicity in humans. (See comment 3.)

3. The Panel recommended dosages for children under 2 years of age for docusate calcium and docusate sodium. The agency, however, in the tentative final monograph for OTC laxative drug products (50 FR 2124 at 2148) proposed that dosages for children under 2 years of age not appear in the OTC labeling because of the concern that constipation in infants may be a sign of a more serious condition that should be properly diagnosed by a doctor. Therefore, dosages for children under 2 years of age for docusate calcium and docusate sodium are being included in this tentative final monograph only under professional labeling.

4. The Panel recommended docusate sodium and senna concentrate as a permitted active ingredient combination (40 FR 12902 at 12921). However, in the tentative final monograph for OTC laxative drug products, the dosages for senna preparations were revised to provide dosages for sennosides A and B only (50 FR 2124 at 2140 and 2141). Therefore, sennosides A and B are being used to describe the combination in this amendment.

The agency has examined the economic consequences of this proposed rulemaking

in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC laxative drug products, is a major rule.

In the economic assessment, the agency also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC laxative drug products is not expected to pose such an impact on small businesses. All conditions reviewed by the Panel are proposed for inclusion in the monograph except one condition that was removed from the market in 1987. Only some minor relabeling will be necessary. This will be a one-time expense when the final monograph is issued. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on laxative drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC laxative drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on OTC laxative drug products containing docusate salts as active ingredients, a period of 120 days from the date of publication of this proposed rule in the Federal Register is being provided for comments and data on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before December 31, 1993, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the ***46595** Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before December 31, 1993. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday

through Friday. Any scheduled hearing will be announced in the Federal Register.

Interested persons, on or before September 2, 1994, may also submit in writing new data demonstrating safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before November 2, 1994. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47740). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addresssed to the Dockets Management Branch (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only comments and data submitted prior to the closing of the administrative record on November 2, 1994. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner of Food and Drugs finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR part 334

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 334 (as proposed in the Federal Register of January 15, 1985, 50 FR 2124) be amended as follows:

PART 334--LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 334 is revised to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Section 334.20 is amended by adding text to read as follows:

§334.20 Stool softener laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in §334.62(d):

(a) Docusate calcium.

(b) Docusate potassium.

(c) Docusate sodium.

3. Section 334.30 is amended by adding new paragraphs (i), (j), and (k) to read as follows:

58 FR 46589-01
(Cite as: 58 FR 46589, *46595)

§334.30 Permitted combinations of active laxative ingredients.

* * * * *

(i) The following stool softener laxative ingredient may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§334.60 and 334.62:

(1) Docusate sodium identified in §334.20(c) and casanthranol identified in § 334.18(c)(1).

(2) Docusate sodium identified in §334.20(c) and phenolphthalein identified in §334.18(g).

(3) Docusate sodium identified in §334.20(c) and sennosides A and B identified in §334.18(h).

(j) The following stool softener laxative ingredient may be combined with the following bulk-forming laxative ingredient provided the combination is labeled according to §§ 34.52 and 334.62: Docusate sodium identified in § 334.20(c) and sodium carboxymethylcellulose identified in §334.10(b)(2).

(k) The following stool softener laxative ingredient may be combined with the following hyperosmotic laxative ingredients provided the combination is labeled according to §§334.54 and 334.62:

(1) Docusate potassium identified in §334.20(b) and glycerin identified in § 334.12(a).

(2) Docusate potassium identified in §334.20(b) and sorbitol identified in § 334.12(b).

4. Section 334.62 is amended by adding text to paragraphs (c) and (d) to read as follows:

§334.62 Labeling of stool softener laxative drug products.

* * * * *

(c) Warnings. In addition to the warnings identified in §334.50(b), the labeling of the product contains the following statement under the heading "Drug Interaction Precaution": "Do not take this product if you are presently taking mineral oil, unless directed by a doctor."

(d) Directions. The labeling of the product contains the following information under the heading "Directions."

(1) For products containing docusate calcium identified in §334.20(a). Adults and children 12 years of age and over: oral dosage is 50 to 360 milligrams. Children 2 to under 12 years of age: oral dosage is 50 to 150 milligrams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(2) For products containing docusate potassium identified in §334.20(b). Adults and children 12 years of age and over: rectal enema dosage is 50 to 250 milligrams in a single daily dose. Children 2 to under 12 years of age: rectal enema dosage is 100 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(3) For products containing docusate sodium identified in §334.20(c). Adults and children 12 years of age and older: oral dosage is 50 to 360 milligrams. Children 2 to under 12 years of age: oral dosage is 50 to 150 milligrams. This

dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

5. Section 334.80 is amended by revising the introductory text and by adding paragraphs (c)(12) and (c)(13) to read as follows:

§334.80 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) contains the following information in addition to the labeling identified in §§334.50, 334.52, 334.54, 334.56, 334.58, 334.60, and 334.62.

* * * * *

(c) * * *

(12) For products containing docusate calcium identified in §334.20(a). Children under 2 years of age: oral dosage is 25 milligrams in a single daily dose or in divided doses.

(13) For products containing docusate sodium identified in §334.20(c). Children under 2 years of age: oral dosage is 20 to 50 milligrams in a single daily dose or in divided doses.

***46596** Dated: August 26, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

(FR Doc. 93-21368 Filed 9-1-93; 8:45 am)

BILLING CODE 4160-01-F

58 FR 46589-01, 1993 WL 332101 (F.R.)
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Citation
51 FR 35136-01
1986 WL 111334 (F.R.)
(Cite as: 51 FR 35136)

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PROPOSED RULES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and **Drug** Administration

21 CFR Part 334

[Docket No. 78N-036L]

Laxative **Drug** Products for Over-the-Counter Human Use; Tentative Final Monograph

Wednesday, October 1, 1986

***35136** AGENCY: **Food** and **Drug** Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The **Food** and **Drug** Administration (FDA) is issuing a notice of proposed rulemaking that amends the tentative final monograph for over-the-counter (OTC) laxative **drug** products by modifying the directions for the use of bulk **laxatives**. This notice is part of the ongoing review of OTC **drug** products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of **Food** and **Drugs** by December 1, 1986. New data relating to the directions for the use of OTC bulk **laxatives** by October 1, 1987. Comments on the new data by December 1, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC **drugs** (21 CFR 330.10). Written comments on the agency's economic impact determination by January 29, 1987.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), **Food** and **Drug** Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:William E. Gilbertson, Center for **Drugs** and Biologics (HFN-210), **Food** and **Drug** Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the Federal Register of March 21, 1975 (40 FR 12902), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative,

antidiarrheal, emetic, and antiemetic **drug** products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic **Drug** Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these **drug** classes. The agency's proposed regulation, in the form of a tentative final monograph, for OTC laxative **drug** products was published in the Federal Register of January 15, 1985 (50 FR 2124). Interested persons were invited to file by May 15, 1985, written comments, objections, or requests for oral hearing before the Commissioner of **Food** and **Drugs** regarding the proposal.

In this amendment to the tentative final monograph, FDA is modifying its position on the directions for use and the dosage of OTC bulk laxative **drug** products that were proposed in Part 334 (50 FR 2124). Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC laxative **drug** products.

In comment 12 of the tentative final monograph (50 FR 2126), the agency stated that some of the Panel's recommendations regarding the directions for use of OTC laxative **drug** products required clarification. The agency stated that where the Panel recommended a daily dose of an ingredient without a dosage interval, the agency was proposing this to mean a single daily dose. However, in reviewing some of the comments submitted in response to the tentative final monograph and in further reviewing the directions for use of marketed bulk laxative **drug** products and the data on these products that were submitted to the Panel, the agency has found that the maximum daily dose of bulk **laxatives** is routinely administered in divided doses rather than as a single dose. In addition, the maximum daily dose of some bulk **laxatives** is so large that it may pose a risk of esophageal obstruction if taken at one time (Ref. 1). This risk can be minimized by administering bulk **laxatives** in divided doses rather than in a single daily dose, as originally proposed by the agency in the directions in the earlier tentative final monograph. The agency also recognizes that OTC bulk laxative ingredients are effective over a wide range of doses and dosing intervals; therefore, the dosages specified in the monograph for these **drug** products should be sufficiently flexible to accommodate the various dosages of marketed products that have been shown to be safe and effective.

Based on a review of the available data and information, the agency is revising the dosage and directions for the use of bulk **laxatives** that were previously proposed in § 334.52(d) (2), (3), (4), (5), (6), and (7) of the tentative final monograph. The dosages being proposed for children are based on the relationship of 1 dose for an adult; 1/2 the adult dose for children 6 to under 12 years of age; and 1/4 the adult dose for children 2 to under 6 years of age. Pediatric dosages for particular ingredients have been proposed only when there is a marketing history of these ingredients being administered to childern in these age groups. For example, an ingredient without a marketed pediatric dosage for children 2 to under 6 years of age will not have a dosage for this age group in the tentative final monograph.

The agency believes that these revised dosages and directions for use provide for necessary flexibility in developing appropriate directions for the wide

[illegible]ge of OTC bulk laxative **drug** products.

Reference

(1) Brunton, L. L., "**Laxatives**," in "The Pharmacological Basis of Therapeutics," 7th Ed., edited by L. S. Goodman, A. Gilman, T. W. Rall, and F. Murad, The MacMillan Publishing Co., New York, pp. 996-997, 1985.

Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information relating to the directions for the use of OTC bulk laxative ingredients by folllowing the procedures outlined in the agency's policy statement published in the Federal Register of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC **drug** review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC **drug** review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC laxative **drug** products, is a major rule.

The agency has determined that under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

***35137** Interested persons may, on or before December 1, 1986, submit to the Dockets Management Branch (HFA-305), **Food** and **Drug** Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before January 29, 1987.

Interested persons, on or before October 1, 1987, may also submit in writing new data relating to the directions for the use of OTC bulk **laxatives**. Written comments on the new data may be submitted on or before December 1, 1987. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC **drugs**, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified wi[illegible] the docket number found in brackets in the heading of this document. Data

and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Data and comments submitted in response to this amendment will be considered by the agency in establishing a final monograph. Data submitted after the closing of the administrative record on December 1, 1987 will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 334

OTC **drugs** Laxative **drug** products.

Therefore, under the Federal **Food, Drug,** and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 334 (proposed in the Federal Register of January 15, 1985; 50 FR 2124) as follows:

PART 334--LAXATIVE **DRUG** PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for Part 334 continues to read as follows:

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.11.

2. In Subpart B, § 334.52 is amended by revising paragraphs (d)(2), (d)(3), (d)(4), (d)(5), (d)(6), and (d)(7), to read as follows:

§ 334.52 Labeling of bulk-forming laxative **drug** products.

* * * * *

(d) * * *

(2) For products containing bran identified in § 334.10(a). Adults and children 12 years of age and over: Oral dosage is up to 14 grams daily in divided doses of 1 to 7 grams per dose. Children 6 to under 12 years of age: Up to 7 grams daily is divided doses of 1 to 3.5 grams per dose. Children 2 to under 6 years of age: Up to 3.5 grams daily in divided doses of 1 to 1.75 grams per dose. Children under 2 years of age: Consult a doctor.

(3) For products containing methylcellulose and sodium carboxymethylcellulose identified in § 334.10(b) (1) and (2). Adults and children 12 years of age and over: Oral dosage is up to 6 grams daily in divided doses of 0.45 to 3 grams per dose. Children 6 to under 12 years of age: Up to 3 grams daily in divided doses of 0.45 to 1.5 grams per dose. Children under 6 years of age: Consult a doctor.

(4) For products containing karaya identified in § 334.10(c). Adults and children 12 years of age and over: Oral dosage is up to 14 grams daily in

divided doses of 3.5 to 7 grams per dose. Children under 12 years of age: Consult a doctor.

(5) For products containing malt soup extract identified in § 334.10(d). Adults and children 12 years of age and over: oral dosage is up to 64 grams daily in divided doses of 3 to 32 grams per dose. Children 6 to under 12 years of age: Up to 32 grams daily in divided doses of 3 to 16 grams per dose. Children 2 to under 6 years of age: Up to 16 grams daily in divided doses of 3 to 8 grams per dose. Children under 2 years of age: Consult a doctor.

(6) For products containing polycarbophil identified in § 334.10(e). Adults and children 12 years of age and over: Oral dosage is up to 4 grams daily in divided doses of 1 gram per dose. Children 6 to under 12 years of age: Up to 2 grams daily in divided doses of 0.5 grams per dose. Children 2 to under 6 years of age: Up to 1 gram daily in divided doses of 0.5 grams per dose. Children under 2 years of age: Consult a doctor.

(7) For products containing any psyllium ingredient identified in § 334.10(f). Adults and children 12 years of age and over: Oral dosage is up to 30 grams daily in divided doses of 2.5 to 7.5 grams per dose. Children 6 to under 12 years of age: Up to 15 grams daily in divided doses of 2.5 to 3.75 grams per dose. Children under 6 years of age: Consult a doctor.

Dated: August 9, 1986.

Frank E. Young,

Commissioner of **Food** and **Drugs**.

[FR Doc. 86-22150 Filed 9-30-86; 8:45 am]

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51 FR 35136-01, 1986 WL 111334 (F.R.)
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federal register

Tuesday
January 15, 1985

Part II

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 334

Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 334

[Docket No. 78N-036L]

Laxative Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) laxative drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal deals only with laxative drug products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by May 15, 1985. New data by January 15, 1986. Comments on the new data by March 17, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determinations by May 15, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the Federal Register of March 21, 1975 (40 FR 12902), FDA published, under 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC laxative, antidiarrheal, emetic, and antiemetic drug products, together with the recommendations of the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Drug Products, which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by June 19, 1975. Reply comments in response to comments filed in the initial comment period could be submitted by July 19, 1975.

In a notice published in the Federal Register of March 21, 1980 (45 FR 18398), the agency advised that it had reopened the administrative record of OTC laxative drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the date the administrative record previously had officially closed. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. Data and information received after the administrative record was reopened have also been put on display in the Dockets Management Branch.

In response to the advance notice of proposed rulemaking, comments were received from 44 drug manfacturers, 2 trade associations, 3 consumers, 1 State government, and 1 university. Copies of the comments received are also on public display in the Dockets Management Branch.

The advance notice of proposed rulemaking, which was published in the Federal Register on March 21, 1975 (40 FR 12902), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the present document is designated in the OTC drug review regulations as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 334 (21 CFR Part 334), FDA states for the first time its position on the establishment of a monograph for OTC laxative drug products. Final agency action on laxative drug products will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC laxative drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC laxative drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the Federal Register of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the Federal Register. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e.,

nditions that would cause the drug to
n[illegible]rally recognized as safe and
e [illegible]to be misbranded, may be
tially introduced or initially delivered
introduction into interstate
mmerce unless they are the subject of
approved new drug application
DA). Further, any OTC drug products
bject to this monograph that are
packaged or relabeled after the
fective date of the monograph must be
compliance with the monograph
gardless of the date the product was
itially introduced or initially delivered
r introduction into interstate
mmerce. Manufacturers are
couraged to comply voluntarily with
e monograph at the earliest possible
te.

In the advance notice of proposed
lemaking for OTC laxative drug
oducts (published in the **Federal**
egister of March 21, 1975; 40 FR 12902),
e agency suggested that the conditions
cluded in the monograph (Category I)
effective 30 days after the date of
blication of the final monograph in the
ederal Register and that the conditions
cluded from the monograph (Category
) be eliminated from OTC drug
oducts effective 6 months after the
ate of publication of the final
o aph, regardless of whether
rther testing was undertaken to justify
eir future use. Experience has shown
at relabeling of products covered by
e monograph is necessary in order for
anfacturers to comply with the
onograph. New labels containing the
onograph labeling have to be written,
rdered, received, and incorporated into
manufacturing process. The agency
determined that it is impractical to
ect new labeling to be in effect 30
s after the date of publication of the
l monograph. Experiences has
wn also that if the deadline for
beling is too short, the agency is
lened with extension requests and
ated paperwork.

In addition, some products will have
be reformulated to comply with the
onograph. Reformulation often
volves the need to do stability testing
n the new product. An accelerated
ging process may be used to test a new
ormulation: however, if the stability
esting is not successful, and if further
eformulation is required, there could be
further delay in having a new product
vailable for manufacture.

The agency wishes to establish a
eas[illegible]e period of time for relabeling
an[illegible]mulation in order to avoid an
innecessary disruption of the
narketplace that could not only result in
conomic loss, but also interfere with
onsumers' access to safe and effective
drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of February 8, 1973 (38 FR 3614) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

The Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic and Antiemetic Drug Products recommended that dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, and dioctyl sodium sulfosuccinate (docusate salts) be classified in Category I as stool softener laxatives at adult oral dosages of 50 to 360 mg within a 24 hour period (see 40 FR 12912). However, after the Panel's report had been submitted, FDA became aware of information in animal studies raising questions about the Panel's conclusions and recommendations for these laxative ingredients (Ref. 1).

The time necessary to complete a full review and evaluation of these new studies could result in a considerable delay in the publication of the tentative final monograph for OTC laxative drug products. Accordingly, the agency has decided to remove all discussion of the safety and effectiveness of docusate salts from this document. The agency intends to publish a separate document in the **Federal Register** addressing the status of these ingredients.

Reference

(1) Teratology studies submitted to NDA 10-586.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments

1. Two comments contended that FDA does not have the authority to establish substantive rules.

The agency responded to these comments in paragraph 4 of the preamble to the tentative final order for emetic active ingredients which was published in the **Federal Register** of September 5, 1978 (43 FR 39544) and reaffirms that response.

2. Several comments urged a greater role for pharmacists in the sale of OTC drug products. One comment recommended that OTC drug products be available only through pharmacies, and two suggested that any labeling suggesting consultation with a physician should mention a pharmacist as an alternative.

The agency responded to these comments in paragraph 5 of the preamble to the tentative final order for antiemetic active ingredients which was published in the **Federal Register** of July 13, 1979 (44 FR 41065) and reaffirms that response.

3. One comment stated that the Panel recommendations violate the objectives and philosophy of the OTC drug review in that the Panel appeared to be intent on undermining the concept of self-medication with OTC laxatives and that it failed to discharge its obligations by placing a number of long established laxative ingredients and laxative combinations in Category III.

The comment provided no basis for its statements. The Panel's recommendations for OTC laxative drug products are fully in accord with the objectives of the OTC drug review as stated in the applicable regulations (21 CFR Part 330). By placing laxative ingredients or combinations in Category III, the Panel simply concluded that the available data were insufficient to permit final classification at the time the Panel reviewed these drugs.

4. One comment objected to the Panel's recommendation that the quantity of each active ingredient be stated in OTC drug product labeling, on the basis that section 502(e)(1)(A) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352(e)(1)(A)) provides for quantitative ingredient labeling only for prescription drug products.

FDA responded to this objection in paragraph 1 of the preamble to the tentative final order for emetic active ingredients (43 FR 39544) and reaffirms that conclusion.

5. Several comments objected to the Panel's recommendation that all inactive ingredients be listed on the labeling, arguing that such a listing would be meaningless, confusing, and misleading to most consumers.

The agency responded to these comments in paragraph 2 of the

preamble to the tentative final order for [illegible]tic active ingredients (43 FR 39544) and reaffirms that response.

6. One comment noted that on several pages of the Panel's recommended monograph the abbreviation "gm" is used for gram, yet 21 CFR 201.62(l) (formerly 21 CFR 1.102(d)) states that the only abbreviation that may be used for gram is "g".

The situation outlined in the comment was an editorial oversight. The OTC drug labeling regulations cited in the comment permit the use of "g" as the only abbreviation for gram. For clarity, metric units have been fully written out in this tentative final monograph.

B. General Comments on Laxatives

7. One comment noted that the product, Nature's Remedy Candy Coated, had been omitted from the "Data and Information Submissions" section of the Panel's report (40 FR 12903) and requested that this omission be corrected.

As noted by the comment the product was inadvertently omitted from the list of submitted products, but the product was considered by the Panel in reaching its conclusions on OTC laxative drug products.

8. A comment stated that the Panel report was generally "antilaxative" in attitude.

It was the intent of the Panel to set forth reasonable standards for the use of OTC laxatives. The Panel believed that many peopld have misconceptions about normal bowel function, particularly a fear of dire consequences if the bowel is not evacuated daily. The Panel believed that this fear is unfounded and leads to certain amount of unnecessary use of laxatives.

9. Comments stated that the Panel was confused on the role of OTC laxative medicines. The comments noted that it was the Panel's opinion that simple constipation could be corrected by a proper diet, and that there are few vaild indications for the use of laxatives. The comments stated that the Panel confused the prevention and medical treatment of constipation with its symptomatic relief. Contending that a consumer considering the use of an OTC laxative is suffering from constipation and is seeking relief through self-medication, the comments stated that it is not responsive to tell the consumer how the condition might have been prevented by eating proper foods or drinking more fluids. The consumer simply wants a laxative that will relieve the existing discomfort safely and effectively. The comments concluded that this overview of constipation was inappropriate.

One of the purposes of the Panel's general discussion was to present a broad view of the problem of constipation. The Panel recognized that prevention of a medical condition or disease is preferable to symptomatic relief, and the discussion of diet, adequate fluid intake, and exercise provides guidance to consumers on how to avoid or reduce constipation. The Panel believed, and the agency agrees, that the public ought to understand that the use of all laxatives should be minimized.

10. Comments stated that the Panel went beyond its charter in making statements concerning the advertising of laxative products, and that such statements regarding OTC laxative advertising were not only based upon inadequate information, but also were highly inappropriate for inclusion in a scientific report.

The OTC drug review procedures do not preclude a panel from expressing its concern about OTC drug advertising. The Federal Trade Commission (FTC) has the primary responsibility for regulating OTC drug advertising. FDA does, however, have the authority to regulate OTC drug advertising that constitutes labeling under the Federal Food, Drug, and Cosmetic Act. Under the act, a manufacturer can be prohibited from advertising a drug to treat a condition for which there are no adequate directions for use on the label. See, e.g., *United States* v. *Article of Drug . . . B-Complex Cholinos Capsules,* 362 F. 2d 923 (3d Cir. 1966); *V.E. Irons, Inc.* v. *United States,* 244 F. 2d 34 (10th Cir.), *cert. denied,* 354 U.S. 923 (1957). In addition, for an OTC drug to be generally recognized as safe and effective and not misbranded, the advertising for the drug must satisfy the FDA regulations at § 330.1(d) (21 CFR 330.1(d)), which state that the advertising may prescribe, recommend, or suggest the drug's use only under the conditions stated in the labeling.

11. Several comments objected to the Panel's statement that "the Panel found no evidence for claims that any laxative has a particular advantage for individuals simply on the basis of sex, age, or other demographic characteristics." (See 40 FR 12905.) The comments suggested that this sentence should not be interpreted as precluding a manufacturer's directing a promotional effort toward a particular demographic group of potential users, and that if a product has characteristics that may be preferred by a significant portion of a demographic group, then truthful statements to that effect should be allowed.

The agency agrees with the Panel. No evidence has been presented to justify labeling claims that any laxative has a particular advantage for individuals simply on the basis of sex, age, or other demographic characteristics. Nor is the agency aware of any characteristics of laxative products, e.g., form, taste, convenience, relative mildness, that may be preferred more by a significant portion of one demographic group than another. Such characteristics should be applicable regardless of the user of the product. However, the agency has no objection to manufacturers directing a promotional effort toward a particular demographic group of potential users as long as there is no claim of a particular advantage based on demographic characteristics.

12. A comment suggested that the monograph set specific dosages rather than express dosage requirements in terms of daily dose limits or ranges. The Comment further contended that the number of dosage units that could be used to deliver the required amount of ingredient did not have to be stated in the monograph. The comment cited as an example an ingredient whose daily dosage limit is 100 milligrams (mg) and stated that a recommended dosage of two 50-mg capsules once a day could be in compliance with the monograph, but that this specific dosage direction need not be in the monograph.

Some of the Panel's recommended dosages require clarification. For example, where the Panel recommended a daily dose of an ingredient without a dosage interval, the agency has clarified this to mean a single daily dose.

The monograph will not specify the number or type of dosage units, i.e., one or more tablets, capsules, teaspoons, needed to deliver the required amount of an active ingredient. Manufacturers will generally be free to choose whether a product should deliver the necessary amount of ingredient(s) in one or more dosage units.

13. Comments stated that the Panel's recommended labeling requirements when added to the general labeling requirements for OTC drugs, will result in a crowded and potentially confusing label that could defeat its intended purpose of informing the layman. Some of the comments stated that it would be very difficult to include all of the required information on the labeling of small size packages. One comment urged the Commissioner to carefully consider the need for each recommended statement with a view to eliminating or modifying the unessential statements.

The labeling of an OTC drug must ontain information essential for the af ad effective use of the drug by the o Labeling should not be eedlessly crowded or confusing and, nerefore, the agency has consolidated r deleted the Panel's recommended abeling wherever possible. The agency elieves that any additional labeling tatements proposed for laxative roducts will not be so numerous as to onfuse the consumer. In addition, anufacturers are free to design ways f incorporating all required information n the package labeling, e.g., by using ap labels or redesigning packages.

14. One comment objected to the anel's recommended indication for axatives in proposed § 334.50(a)(1) "for ne short-term relief of constipation". he comment argued that the phrase short-term" duplicates the information rovided in proposed § 334.50(c)(3), vhich warns against using OTC axatives for longer than 1 week. The omment also argued that "short-term" efers to the period of laxative use and ot to the degree of effectiveness of the axative. Concluding that it was naccurate and unnecessary to identify axative products for "short-term relief," he comment recommended deleting short-term" from the indication.

agency agrees that "short-term" ho.d refer to the period of laxative use nd not to the degree of effectiveness. he agency also agrees that the 1-week se limitation warning adequately lefines the period of time an OTC axative may be used. The Panel utilized he phrase "short-term" in an attempt to ualify the indication for OTC laxatives, vhich are intended for the relief of asional constipation and not in ting chronic constipation. Chronic stipation may be a sign of a serious dition that requires diagnosis and tment by a doctor. Therefore, the ication in the tentative final nograph does not include the phrase ort-term." and the indication is evised to state "For the relief of ccasional constipation."

15. comments objected to the Panel's iew that the labeling claims irregularity" and "regularity" are isleading. The Comments contended hat these terms are readily understood y the consumer, that they serve a substitute for the socially unacceptable erm "constipation," and that there is neither a practical nor a legal basis for anning their use.

The agency agrees with the comment ha' erm "irregularity" should be nc n the monograph. The term as been widely used in the labeling and dvertising of laxative drug products nd is a term consumers readily understand. In addition, according to Webster's New Collegiate Dictionary (Ref 1) "irregularity " is synonymous with the term "constipation." Therefore, the agency has no objection to its use and is proposing its use in the tentative final monograph. However, the agency agrees with the Panel that the term "regularity" is inappropriate for use in the labeling of OTC laxative drug products. "Regular" is defined as recurring or functioning at fixed or uniform intervals (Ref. 1). When used in the context of bowel habits, the term "regularity" implies that laxatives are necessary to maintain an acceptable frequency of bowel movements. Because there is a normal range of frequency from three bowel movements a day to three per week (Ref. 2), "regular" bowel movements are not essential to health or well-being. Therefore, the agency agrees with the Panel that the term "regularity" is Category II.

References

(1) "Webster's New Collegiate Dictionary," G. & C. Merriam Co., Springfield, MA 1979, s.v. irregularity and regular.

(2) Connell, A.M., et al., "Variation of Bowel Habit in Two Population Samples," *British Medical Journal, 2:1095–1099, 1965.*

16. A comment took issue with the following statements in the Panel's report: "The Panel has no objection to statements regarding the source of the laxative ingredient. However, the suggestion that a laxative is somehow 'natural' because of its source is misleading, because it implies that the product or ingredient is a 'natural way' to induce laxation. It is not considered 'natural' to take any laxative." The comment argued that manufacturers should have the right to make truthful statements about the source of their products, i.e., that an ingredient is from a natural source if that is the case. The comment stated that the determination whether such a statement is misleading must be made within the total context of its use. Another comment stated that bran-rich cereals are natural laxatives, and their consumption is a natural way to provide the bulk in the diet that is necessary for normal laxation.

The agency agrees that a manufacturer should be allowed to make truthful statements in its labeling about the source of a laxative ingredient contained in the product. If an ingredient is in fact from a natural source, then there is no reason why such information may not appear in the labeling of the product so long as this information is not presented in such a way as to imply that it confers any advantage to the product in terms of safety or effectiveness or in any way encourages frequent or prolonged use of laxatives. The agency agrees with the comment that a determination as to whether such a statement is misleading must be made within the context of its use. It is the responsibility of the manufacturer to use information regarding the source of a product ingredient in a way that is not misleading.

17. Stating that many laxative products are prepared from unsterilized natural sources or contain ingredients that readily support microbiological growth, a comment urged that appropriate safety tests for contaminants like salmonella and staphylococcus be required for laxative drug products composed in whole or in part of natural ingredients.

The agency agrees with the comment; all drug products should be free from microbiological contamination. Manufacturing guidelines for preventing microbiological contamination are covered by the Current Good Manufacturing Practice Regulations (CGMPR) (21 CFR Part 211), and all OTC drug products are required to be manufactured in compliance with these regulations. The specific provisions of these regulations concerning the prevention of microbiological contamination are contained in 21 CFR 211.84(d)(6) and 211.113.

18. A comment stated that any regulation that purports to ban truthful and clearly understood alternative language in consumer labeling is arbitrary and capricious, and that such limitation is not authorized by the enabling statutes. The comment also urged that statements describing product attributes should not be regulated by OTC drug monographs.

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through

petitions to amend monographs under § 330.10(a)(12). For example, the labeling proposed in this tentative final monograph has been expanded and revised in response to comments received.

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to assist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544). The agency's decision on this matter will be announced in the **Federal Register** following conclusion of its review of the material presented at the hearing.

Claims concerning nontherapeutic characteristics of drugs ("tastes good") or those unrelated to the characteristics of the drug itself ("4 out of 5 doctors recommend") are not dealt with in OTC drug monographs. Labeling claims of this type are, however, subject to regulatory actions initiated under the drug misbranding provisions of section 502 of the act (21 U.S.C. 352).

19. A comment suggested that recommended § 334.50(a)(1) be revised to read, "The labeling shall identify the product as a laxative (or other term of similar import)," and suggested "constipation remedy" or "for relief of constipation" as commonly understood and truthful alternatives that should be permitted.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in OTC drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The term "remedy" has been used for many years to describe various OTC drug products. The agency believes this term is unrelated to the characteristics of the drug in question and, therefore, does not relate in a significant way to the drug's safe and effective use. Accordingly, the term is outside the scope of the OTC drug review. Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading.

Moreover, any statement or term that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, statements and terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

The phrase "for relief of constipation" is more appropriately an indication and the agency is proposing the indication "for relief of occasional constipation" in the indications section of this tentative final monograph. (See comment 14 above.)

20. A comment suggested that the Panel's definition of laxative, i.e., "any agent used for the relief of constipation," was too broad and could be misunderstood, especially when applied to stool softener and lubricant laxatives. According to the comment, the term "laxative aid" should apply to substances that act solely to modify the fecal contents and thereby aid or facilitate a laxative response; while the term "laxative" should apply only to agents that act upon the myoneural structures of the intestinal tract. The comment concluded that the terms "laxative" and "laxative aid" would more precisely set forth the pharmacologic activity of these different drugs.

The Panel's definition of laxative as "any agent used for the relief of constipation" includes all of the various mechanisms of action of OTC laxatives. The intended effect of these products is always laxation, even though this effect is achieved by different actions. Subdividing laxative ingredients into laxative and laxative aids would not be helpful and could be confusing to the consumer. The statements of identify, e.g. "bulk-forming," "stool-softener," etc. which will appear on the product's labeling, will adequately inform the consumer as to the product's characteristics. Therefore, a change to the definition of laxative is unnecessary.

21. A comment stated that it was not clear whether the labeling information in the professional labeling section (recommended § 334.80) is meant to supplement the labeling required for the OTC labeling of laxative products or is meant to be the only information required for health professionals. The comment argued that many warnings in recommended §§ 334.50 through 334.64 are unnecessary for health professionals, that recommended § 334.80 should specify that only the information contained in the professional labeling section need be provided to health professionals, and that information such as mode of action and definitions should be omitted from professional labeling, because health professionals should understand this information.

A similar issue was discussed in comment 56 of the preamble to the Antacid Tentative Final Monograph, published in the **Federal Register** of November 12, 1973 (38 FR 31264). There, the agency stated that the warning statements appearing on OTC products should be included in professional labeling. The health professional needs this information in order to best advise the consumer as to the safe and effective use of laxative drug products. Thus, the agency tentatively concludes that labeling intended for health professionals must include all labeling required for OTC products as well as the specialized professional labeling. The monograph has been amended accordingly.

22. A comment objected to the Panel's terms for classifying the mechanism of action of laxatives, stating that these terms are obsolute, confusing, and inaccurate. The comment argued that because most laxatives attract water into the stool, a laxative should be defined as any substance that increases water in the stool. The comment further argued that a separate classification is not needed for hyperosmotic, saline, or stool softener laxatives, and that stimulant laxatives do not stimulate anything, but act as the other laxatives. The comment suggested replacing the terms "stimulant," "saline," "hyperosmotic," and "stool softener," which were recommended by the Panel for classifying certain laxatives, with one of the following terms: "hydrophoric" (to carry water), "sodium-water retention," or "sodium-retention laxative." The comment stated

hat these terms more accurately describe the mechanism of action of a a [illegible]p of laxatives, which, amounts o p[illegible]ing sodium and water absorption from the small and large ntestines. The comment added that this group of laxatives could be subclassified nto plant, synthetic, or inorganic chemical groups.

The comment offered no data to support a classification of laxatives based on a particular mechanism of action. Moreover, the Panel stated that he precise mechanisms of action of axatives are unknown. With the exception of the term hyperosmotic, the Panel's recommended terms for classifying laxatives described the general ways in which these laxatives work and are understandable to most consumers. The word "hyperosmotic," which is applicable to only two rectal axatives (glycerin and sorbitol), is probably not well understood by consumers. Consumers are more familiar with the dosage forms of these ngredients (enema and suppository) and the action that can be expected rom these products. Because the word 'hyperosmotic" is not needed and might be confusing, it will not be required on the labeling of these dosage forms. It w[illegible] owever, be retained in the mo[illegible]graph for classification purposes only. The terms proposed by the comment do not appear to be more accurate than those recommended by the Panel, and a subclassification of axative substances into plant, synthetic, and inorganic chemcial groups would not provide consumers with any useful information. Therefore, a [illegible]lassification of laxatives using ferent mechanism-of-action minology does not appear to be rranted and will not be proposed at s time.

23. Numerous comments disagreed th recommended § 334.50(a)(1), which [illegible]quires the labeling of laxatives to contain a statement identifying laxatives based on the action they have in the bowel, e.g., "stimulant laxative," "bulk-forming laxative," etc. The comments argued that identifying laxatives by their specific action is meaningless, confusing, and misleading to consumers, and "does not provide any useful information." Two of the comments also contended that requiring these identity statements in the labeling would violate the regulatory requirement that the identity statement be [illegible]rms that are meaningful to the lay[illegible] and that requiring them was beyond FDA's statutory authority. One of the comments further added that it was not clear whether recommended § 334.50(a)(1) required only the identity statement, e.g., "stimulant laxative," "bulk-forming laxative," etc. to appear on the labeling or whether the definitions of the identity statements, contained in § 334.3, were also required on the labeling. Most of the comments recommended deleting the proposed identity statements; others recommended that laxatives be identified simply as substances or agents that increase the bulk or water content of the stool.

The agency does not agree that the identity statements for laxatives should be deleted from the monograph. Laxatives relieve constipation by various actions, depending on how a specific ingredient works in the bowel. The identity statements, such as "stimulant laxative," "bulk-forming laxative," etc., proposed in § 334.3, describe in nontechnical terms the effect a particular laxative product will have in the bowel or on the stool. Such information is necessary to provide consumers with adequate directions for using OTC laxative products safely and effectively, and is, therefore, within FDA's misbranding authority under section 502(f)(1) of the act (21 U.S.C. 352(f)(1)).

There appears to be no basis for including the definitions for each identity statement in the labeling, as originally recommended in the advance notice of proposed rulemaking in § 334.50(a)(1). The definitions will not increase consumers' understanding of a laxative's activity nor provide information that will increase the safety or effectiveness of OTC laxatives. Rather they may complicate and confuse laxative labeling. Therefore, any reference to definitions has been deleted from § 334.50(a)(1).

The agency has also determined that in addition to needing to know how a laxative acts, consumers should be aware of how soon a laxative is expected to work. Each type of laxative will generally work within a certain time (Refs. 1 and 2). For example, bulk-forming laxatives generally act within 12 to 72 hours; lubricant laxatives generally act within 6 to 8 hours. This information would increase a consumer's ability to properly select and use a particular laxative product. This information will also increase the safety of laxative products because consumers will be more likely to discontinue using a particular product and seek professional assistance if it does not act within a labeled time frame rather than increasing the specified dosage beyond safe and effective OTC levels.

Therefore, the agency is proposing in the laxative tentative final monograph, under the heading "Indications," the following time frames within which the different types of laxatives are expected to produce bowel movement:

Bulk laxatives—12 to 72 hours
Hyperosmotic laxatives—¼ to 1 hour
Lubricant laxatives:
  Oral dosage forms—6 to 8 hours
  Rectal dosage forms—2 to 15 minutes
Saline laxatives:
  Oral dosage forms—½ to 6 hours
  Rectal dosage forms—2 to 15 minutes
Stimulant laxatives:
  Oral dosage forms—6 to 12 hours
  Rectal dosage forms—¼ to 1 hour
Stool softener laxatives:
  Oral dosage forms—12 to 72 hours
  Rectal dosage forms—2 to 15 minutes
Carbon dioxide-releasing suppositories—5 to 30 minutes

References

(1) Darlington, R. C., "Laxative Products," *in* "Handbook of Nonprescription Drugs," American Pharmaceutical Association, 5th Ed., Washington, pp. 40–41, 1977.

(2) Barowsky, H., "A Rectal Suppository for Inducing Lower Bowel Evacuation," *American Journal of Gastroenterology*, 39:183–186, 1963.

24. A comment stated that grouping pharmacologically diverse and clinically contrasting laxatives into single categories has unfairly attributed the undesirable features of one ingredient to all the other ingredients in the group. The comment argued that pharmacologic grouping becomes arbitrary when label warnings, cautions, and limits of safe treatment are imposed for all ingredients of the group rather than on specific ingredients within the group.

In the tentative final monograph general warnings applicable to all laxative ingredients are supplemented by specific warnings for individual ingredients, thereby minimizing the possibility of unfair attribution as suggested in the comment. For example, stimulant laxatives must include all the applicable general warnings for laxatives: but bisacodyl, castor oil, and phenolphthalein (individual stimulant laxatives) must be labeled with additional specific warnings.

25. Several comments contended that the Panel's recommended 1-week use limitation warning (§ 334.50(c)(3)) is irrational, arbitrary, and unwarranted. The comments argued that the panel did not provide evidence that laxatives are harmful if taken for longer than 1 week. The comments also pointed out that the Panel recognized that laxative therapy may be necessary for longer than 1 week in some elderly persons and in persons on low fiber diets. Some of the comments recommended that the 1-

week limitation be changed to a "prolonged use" limitation. Others [illegible]y recommended deleting it.

The agency considers the recommended 1-week limitation on the use of laxatives to be a necessary warning for the safe use of these products. The comments provided no data to indicate that any other time restriction would be more appropriate. The suggestion to replace the proposed limitation with a "prolonged use" limitation is unacceptable. "A prolonged use" limitation would be defined differently by different people; some might interpret it to mean 1 week, others as continuous use over a year or longer. Constipation lasting longer than 1 week could signify a more serious condition, such as deverticular disease of the colon, irritable bowel, or cancer of the colon. In such cases it is essential that the person see a doctor at the earliest possible time so that the condition can be diagnosed and correctly treated. However, in some situations the long-term use of laxatives may be necessary, e.g., in some elderly persons suffering from certain disease conditions and in persons with heart ailments or other conditions where straining should be avoided. In these cases, laxative therapy should be carried out under the care and direction of a doctor so that regular therapy can be prescribed and the person's condition monitored regularly. Therefore, the agency proposes to retain the 1-week use limitation warning.

26. One comment suggested that the definition of "short-term use" (i.e., "use of a laxative for no longer than a 1-week period") in recommended § 334.3(k) should be revised by adding the word "daily" after the word "laxative" to define more explicitly "short-term use."

The definition of "short-term use" in § 334.3(k) as originally recommended has been deleted in this tentative final monograph. The use limitation warning (proposed § 334./50(b)(3) of the monograph) adequately explains the period of "short-term use;" therefore a definition of "short-term use" has not been included in the monograph.

27. Several comments stated that the signal word "warning" is too strong for the types of cautionary statements required for laxative products and suggested that the term "caution" be used instead. The comments argued that the word "warning" should be used only to highlight imminent physical hazards associated with normal storage or use of such consumer products as household cleaners, polishes, insecticides, and packaging forms such as aerosols. The comments suggested that the signal word " caution" in recommended §§ 334.50, 334.52, 334.54, 334.56, 334.60, 334.62, and 334.64.

Section 502(f)(2) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352 (f)(2)), states, in part, that any drug marketed OTC must bear in labeling ". . . such adequate warnings . . . as are necessary for the protection of users." Section 330.10(a)(4(v) of the OTC drug regulations provides that labeling of OTC drug products should include warnings against unsafe use, side effects, and adverse reactions. . . ."

The agency notes that historically there has not been a consistent usage of the signal words "warning" and "caution" in OTC drug labeling. For example, in §§ 396.20 and 396.21 (21 CFR 369.20 and 369.21), which list "warning" and "caution" statements for drugs, the signal words "warning" and "caution" are both used. In some instances, either of these signal words is used to convey the same or similar precautionary information.

FDA has considered which of these signal words would be most likely to attract consumers' attention to that information describing conditions under which the drug product should not be used or its use should be discontinued. The agency concludes that the signal word "warning" is more likely to flag potential dangers so that consumers will read the information being conveyed. Therefore, FDA has determined that the signal word "warning," rather than the word "caution," will be used routinely in OTC drug labeling that is intended to alert consumers to potential safety problems.

28. A comment suggested that the phrase "this product" in two of the warnings recommended by the Panel in § 334.50(c) (1) and (3) should be replaced by "laxatives" or "laxative products" to avoid creating the implication that these warning statements are applicable only to particular product. The comment noted that these warnings applied equally to all laxative products.

The agency agrees with the comment that these warnings apply to all laxative products. Accordingly, "laxative products" has been used instead of "this product" in proposed § 334.50(b) (1) and (3) of the monograph.

29. A comment recommended that the warning statements in recommended § 334.50(c) (2) and (3), "If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a physician before using a laxative," and "This product should not be used for a period of longer than 1 week except under the advice and supervision of a physician," should be combined and reworded for clarity and brevity as follows: "A laxative should not be used longer than 1 week, except upon the advice of a physician. If a sudden change in bowel habits persists longer tha 14 days, a physician should be consulted."

The agency disagrees that these specific warnings should be combined. Two important and distinct issues are identified in these warnings, and each one should be treated separately. Patients who have noticed a change in bowel habits that has persisted for at least 2 weeks are instructed not to use a laxative at all without first consulting a physician. Patients who have temporary constipation are warned not to use the product for more than 1 week. If at the end of that time their bowel function has not returned to normal, they are instructed to consult a physician.

30. A comment suggested that the warning recommended by the Panel in § 334.50(c) (2), "If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a physician before using a laxative," be changed to allow 1 month for change in bowel habits. The comment argued that 2 weeks is the normal duration of "ordinary intestinal upset," and the warning with an interval of only 2 weeks would cause unnecessary apprehension among many consumers.

The agency disagrees that the 2-week period in this warning should be changed to 1 month. Changes in regular bowel habits that persist for 2 weeks may be a sign of a serious underlying medical illness that requires diagnosis and care by a doctor. The comment provided no data demonstrating that "ordinary intestinal upset" usually lasts 2 weeks or any medical justification for extending the 2-week period to 1 month.

31. A comment suggested that croton seed oil and the kukula nut of Hawaii could be investigated for their laxative effect.

This suggestion is outside the scope of the OTC drug review process, which is intended to determine those ingredients that are generally recognized as safe and effective for OTC use. The comment included no data to substantiate the safe and effective use of these ingredients as OTC laxatives nor is the agency aware of such data. Investigation of new laxative agents is the responsibility of the drug industry, not FDA.

C. Comments on Bulk-Forming Laxatives

32. One comment objected to the Panel's definition of a bulk-forming laxative because the comment was not aware of bulk-forming laxatives

increasing bulk volume and water either more or less than other laxatives.

The Panel defined a bulk-forming laxative in recommended § 334.3(c) as an agent that promotes the evacuation of the bowel by increasing bulk volume and water content of the stools. In defining other types of laxatives, e.g., saline and hyperosmotic, the Panel did not attempt to quantify the amount of water increased in the stool, but only attempted to describe the action that occurs. The agency believes that the Panel's definition of a bulk-forming laxative is accurate.

33. A comment criticized as biased and scientifically unfounded the Panel's opinion that bulk-forming laxatives are among the safest of laxatives. The comment argued that the unsoundness and inconsistency of the Panel's position are illustrated by the Panel's own statement that "conclusive studies testing this hypothesis have not yet appeared". (See 40 FR 12907.)

The Panel, because of its scientific training and experience, had ample expertise on which to base an opinion that bulk-forming laxatives are among the safest of laxatives. The Panel's reasons for this opinion are that bulk-forming laxatives are not generally absorbed from the digestive tract, and they increase the frequency of bowel movements and soften stools by holding water in the stool. The Panel cited bran as a good bulk-forming laxative, when accompanied with adequate fluid intake. The comment offered no evidence to support its statement that the Panel's opinion is scientifically unfounded, nor is the agency aware of any scientific data inconsistent with the Panel's statement. The Panel's statement that "conclusive studies testing this hypothesis have not yet appeared" was taken out of context by the comment. This statement is part of the Panel's comments on relationships between intraluminal pressure (p), tension of the bowel wall (t), and the radius of the bowel lumen (r), referred to as the Law of LaPlace. It was this relationship ($P = t/r$) about which the Panel stated that conclusive studies testing this hypothesis have not yet appeared.

34. Numerous comments stated that considering the safety of bulk-forming laxatives and their proven and potential benefits for various indications, there is no rational basis for restricting their unsupervised use to 1 week as recommended by the Panel in § 334.50(c)(3) or for characterizing them as appropriate only for short-term use as recommended in § 334.50(a)(1). The comments noted that these labeling requirements as applied to bulk-forming laxatives were not supported by a recommendation in the Panel's report. The comments also indicated that dietary bran and other bulk laxatives are essentially food derivatives that replace fiber in many diets, and as such are necessarily fit for longer use. Therefore, the comments concluded that bulk-forming laxatives should be exempt from the labeling in recommended § 344.50 (a)(1) and (c)(3).

Some of the ingredients in bulk-forming laxative drug products, especially those that are present at comparable levels in foods, may be ingested for periods of longer than 1 week without risk of untoward health effects. However, the agency believes that a decision that any laxative product should be used for longer than 1 week should be made by a doctor.

As discussed in comment 25 above, constipation lasting for longer than 1 week could be a sign of a more serious condition for which proper diagnosis and treatment may be warranted. Therefore, the 1-week use limitation warning will be retained for bulk-forming laxatives as well as all other OTC laxative drug products. The agency wishes to emphasize however, that this limitation is applicable only to laxative drug products and in no way applies to or is intended to reflect on the safety of any high fiber foods or food supplements such as bran or bran cereal.

35. Several comments pointed out that when the agency revoked the general warning requirement for OTC drugs in 21 CFR 330(i), i.e., "Warning: Do not take this product concurrently with a prescription drug except on the advice of a physician" (40 FR 11717), it stated that a general warning often goes unheeded and that a specific statement for a drug or class of drugs will be more effective. The comments stated that the Panel's suggested warning in § 334.52(b) for bulk laxatives derived from cellulose is virtually identical to this general warning and therefore is inappropriate. One comment asked that the reference to prescription drugs in this warning be replaced with the specific drugs that have been noted to react with bulk laxative ingredients. These drugs are digitalis, nitrofurantoins and salicylates. Two comments pointed out that the Panel stated that the clinical significance of the interaction between cellulose derivatives and these three drugs has not been established. Therefore, the warning should be deleted. In any case, the comments further suggested that when a specific drug interaction precaution is justified, it should be worded in such a manner as to allow a physician to override the warning.

The agency agrees that a specific warning statement is preferable to a general statement when a clinically significant adverse effect can be attributed to a specific drug. However, as the Panel stated in its report (40 FR 12907), the clinical significance of the interaction between digitalis, nitrofurantoins, and salicylates has not been determined. After evaluating several references concerning the reported interaction between these three drugs and cellulose derivatives, the agency tentatively concludes that these data do not warrant requiring a warning on the OTC labeling of cellulose derivative bulk laxatives (Refs. 1, 2, and 3). Johnson et al. (Ref. 1) and Kasper et al. (Ref. 2) report that the mean peak plasma concentration of digoxin taken following a dietary fiber, such as cellulose, does not vary significantly compared with digoxin when it is taken alone. The time for digoxin to reach its mean peak plasma concentration is longer when digoxin is taken following the ingestion of a dietary fiber. However, the clinical effects of the drug are not substantially altered. Seager (Ref. 3) suggests a similar occurrence with nitrofurantoins. Because the interaction between cellulose derivatives and other drugs does not appear to be clinically significant, the warning has not been included in this tentative final monograph.

References

(1) Johnson, B.F., et al., "Effects of a Standard Breakfast on Digoxin Absorption in Normal Subjects", *Clinical Pharmacology and Therapeutics*, 23(3):315–319, 1978.

(2) Kasper, H., et al., "The Effects of Dietary Fiber on Postprandial Serum Digoxin Concentration in Man," *The American Journal of Clinical Nutrition*, 32:2436–2438, 1979.

(3) Seager, H., "The Effects of Methylcellulose on the Absorption of Nitrofurantoin from the Gastrointestinal Tract," *Journal of Pharmacy and Pharmacology*, 20:968–969, 1968

36. Several comments stated that the phrase "accompanied by adequate liquid intake" should be deleted wherever it appears in recommended § 334.10 for bulk-forming laxatives, and be replaced with a specification of what "adequate" liquid intake is, namely, "the ingestion of a full glass (8 ounces (oz)) of liquid with each dose." In conjunction, the comments requested that the warnings in recommended § 334.52(a)(1) "Drink a full glass (8 oz) of liquid with dose," and in recommended § 334.52(a)(2), for products containing karaya (sterculia gum), "Drink a full

glass (8 oz) of liquid immediately with [illegible]se.", be deleted because these [illegible]s essentially duplicate the labeling in recommended § 334.10. The comments also stated that a direction to drink liquid with each dose is properly part of the directions for use, and is not properly a caution.

The agency agrees with the comments. The phrase "accompanied by adequate liquid intake" in the directions for bulk-forming laxatives is revised to read "Drink a full glass (8 oz) of liquid with each dose." Because the phrase "adequate liquid intake" no longer appears in the labeling, the definition of adequate liquid intake in recommended § 334.3(a) is unnecessary and is not included in this tentative final monograph. The warnings for bulk-forming laxatives in recommended § 334.52(a) (1) and (2) that advised drinking a full glass of liquid with each dose repeat the labeling in § 334.10, and therefore are not included in this tentative final monograph.

37. One comment questioned the scientific basis for requiring in the labeling of certain laxatives that a full glass (8 oz) of water be taken with each dose. The comment contended that the [illegible]uirement was unnecessary because [illegible] volume of fluid exchanged across the intestinal mucosa far exceeds any oral fluid ingestion.

The recommendation in the Panel's report for adequate fluid intake applies only to bulk-forming laxatives. It does not restrict the fluid to water, but calls for the ingestion of a full glass (8 oz) of liquid with each dose (40 FR 12096). The recommendation is part of the labeling that the Panel concluded was necessary for the proper use of bulk-forming laxatives because esophageal obstruction has occurred when bulk-forming laxatives have been swallowed dry, and the possibility exists that fecal impaction or intestinal obstructon may occur if adequate fluid intake is not assured. No data were submitted to show that a smaller amount of liquid, i.e., less than 8 oz of liquid, would be sufficient to prevent the potential dangers described above.

38. A comment recommended that dietary bran, such as is found in bran-rich ready-to-eat breakfast cereals, be specifically excluded from the proposed regulations, and that continued sale and promotion of bran-rich breakfast cereals as mild laxatives be permitted. Another [illegible]ment made the statement that a [illegible]kfast cereal containing bran has for 50 years made laxative claims, and that these claims were permissible as "old drug claims" under the 1938 Food, Drug, and Cosmetic Act.

The meaning of "old drug claims" mentioned in the comment is unclear. Presumably, the commenter is referring to the "grandfather clause" of the 1938 act which exempts certain drugs from regulation as "new drugs" under section 201(p) of the act (21 U.S.C. 321(p)). The "grandfather clause" mentioned in the comment would not apply, however, unless the product in question were a drug. And, even if such a drug product did fall within the "grandfather clause" with respect to the product's status as a new drug, the product would remain subject to the other provisions of the act that apply to drugs. Moreover, to qualify for the "grandfather clause" a product's labeling must have remained unchanged from 1938 to the present time. The comment submitted no evidence that the labeling of these products has remained unchanged since 1938.

The Panel's reference to "dietary gran" has resulted in some confusion, including the impression that all high fiber food products, such as breakfast cereals, would be subject to regulation by the OTC laxative drug monograph. Bran cereals marketed solely as food products are not intended to be subject to regulation by the OTC laxative drug monograph. Therefore, "dietary bran" is not included in this tentative final monograph. The agency is aware, however, that bran has been marketed and labeled for use as a laxative. Therefore, "bran" is included in this tentative final monograph for those products that are marketed as laxative drug products. In order to avoid the impression that all high fiber food products regardless of labeling would be subject to the monograph, the term "bran", rather than "dietary bran" is used in the monograph.

A product that contains bran and that makes a laxative claim is subject to regulation as a drug. To avoid such regulations, it need merely drop the laxative claim. Laxative claims on a food product such as "the modern laxative" would bring the food product within the definition of "drug" in section 201(g)(1)(B) of the act (21 U.S.C. 321 (g)(1)(B)). In the absence of laxative claims, bran cereals and other bran products would be regulated as foods. Claims such as "contains fiber, which provides bulk to the diet," or "food-fiber cereal," generally would be considered to be descriptive statements of the cereal's food properties and would not be considered drug claims.

39. A comment contended that breakfast cereal containing dietary bran is always consumed with milk; therefore, the "adequate liquid intake" labeling in recommended § 334.10 is not necessary. The comment further stated that it is inappropriate to describe a bowl of cereal as a "dose," and suggested that the term "serving" would more completely describe the form in which cereal is consumed.

The required labeling statements for bulk-forming laxative drug products are not intended for breakfast cereals containing dietary bran that are sold as and designed to be consumed as foods. Thus the agency will not require such food products to bear the required labeling statements for bulk-formimg laxatives, including the statement in § 334.10 regarding adequate liquid intake. However, as discussed in comment 38 above, if cereal products contain a drug claim the product is then subject to being regulated as a drug and must then conform to the monograph.

40. A comment stated that bran-rich breakfast cereals are not drugs, and restrictions on advertising that are appropriate for drugs are not appropriate for breakfast cereals. The comment stated that the Laxative Panel disapproved of any mention of a laxative product's good taste. The comment contended that bran-rich breakfast cereals with a laxative claim should not be forced to discontinue the use of "good taste" as an advertising claim.

As discussed in comment 38 above, the agency does not intend that bran cereal food products be subject to regulation by the laxative monograph. The Panel's statements regarding palatability of products concerned drug products. The agency does not object to truthful statements which accurately reflect inherent characteristics of a drug product, but agrees with the panel that they should not be used in a manner to support claims of effectiveness or to promote frequent or continued use.

41. A comment stated that recommended § 334.50(c) (4), (5), and (6), which pertain to the amount of sodium, potassium, and magnesium in the maximum recommended daily dose of a laxative product, should not be applicable to bran-rich cereals. The comment contended that recommended § 334.10 indicated no upper dosage limitation for dietary bran, and as such, recommended § 334.50(c) (4), (5), and (6) would be unworkable. The comments further contended that sodium and magnesium labeling is covered by nutritional labeling under food regulations and that it would be cumbersome and unnecessary to have comply with two sets of labeling on precisely the same elements.

As discussed in comment 38 above, bran-rich breakfast cereals would be

subject to the drug labeling requirements of the laxative monograph only if they make a laxative claim. If a product makes a drug claim there is no reason why that product should be exempt from any requirements applicable to similar drug products. If a bran cereal product wishes to avoid drug labeling requirements it need only avoid making a laxative claim.

42. One comment questioned whether the water-retaining properties of polycarbophil, in vitro, have a correlation with its laxative action.

The Panel presumed that polycarbophil acts by retaining water intraluminally and opposing dehydration in the bowel. The conclusion of effectiveness, however, was based on clinical studies that demonstrated that polycarbophil produced laxation. As stated in the response to comment 22, the exact mechanism by which most laxative agents produce laxation is unknown. Although knowledge of these mechanisms is desirable, it is not essential to a determination of safety and effectiveness.

43. A comment stated that it wanted to clarify that native carrageenan was an emulsifying agent and not an active ingredient of a particular product.

The Panel reviewed native carrageenan as an active ingredient because it was listed on the label of a product submitted for review. The Panel believed that because this ingredient is a hydrocolloid it had potential as a bulk-forming laxative. However, because of the lack of effectiveness data the Panel placed this ingredient in Category III. The agency agrees with the Panel that additional data are necessary before this ingredient can be considered a Category I laxative ingredient. Native carrageenan could be used as an active ingredient (emulsifying agent) because this ingredient is widely used in the food industry as a stabilizer and demulcent. FDA does not object to native carrageenan being included in laxative products as an inactive ingredient. However, its name should not be placed on the label in a manner that would mislead the consumer into thinking that it is an active ingredient.

44. One comment requested that recommended § 334.10(b) "Cellulose derivatives," be revised to include *alpha*-cellulose (powdered cellulose) as a Category I bulk laxative. The comment submitted data (Ref. 1) that, it claimed, demonstrate the safety and effectiveness of *alpha*-cellulose for OTC use as a bulk laxative.

After reviewing all of the available data, the agency believes that the data are inadequate to establish general recognition of safety and effectiveness of *alpha*-cellulose as an OTC laxative ingredient.

As evidenced by the FDA GRAS Food Ingredient Report (FDABF-GRAS-028), cellulose is generally recognized as a safe ingredient. *Alpha*-cellulose undoubtedly has potential as an OTC laxative ingredient, as several semisynthetic celluloses (methylcellulose and sodium carboxymethylcellulose) are already included in the proposed monograph for OTC laxative drug products. However, general recognition of effectiveness has not been demonstrated by the submitted studies. The subjects in the submitted studies were selected on the basis of slowest transit times and lowest daily fecal outputs, and do not meet the definition of constipated subjects (persons with not more than three spontaneous evacuations per week). Because laxatives are intended to relieve constipation, effectiveness cannot be established by studies in asymptomatic individuals.

While it could be argued that *alpha*-cellulose should be included in the monograph because of its similarity to the semisynthetic cellulose derivatives, the agency notes that the dose of the cellulose derivatives recommended by the Panel in the proposed monograph is 4 to 6 g whereas the dose used in the submitted studies was 14 g cellulose plus 6 g pectin. Although the comment concludes that pectin is an inactive ingredient, the difference in the dose of the cellulose is not explained. Therefore, the agency concludes that a clinical study, similar in design to those submitted (but in constipated subjects) is necessary before *alpha*-cellulose can be included in the monograph.

The agency's detailed comments and evaluation on the data and its recommendation for additional studies are on file in the Dockets Management Branch (Ref. 2).

References

(1) Comment No. CP, Docket No. 78N-036L, Dockets Management Branch.

(2) Letter from William E. Gilbertson, FDA, to Harold C. Anderson, Syntex Corporation, ANS LET 009, Docket No. 78N-036L, Dockets Management Branch.

D. Comments on Hyperosmotic Laxatives

45. Several comments requested clarification of the dosage for glycerin suppositories in recommended § 334.12(a). One comment pointed out that the Panel had concluded that glycerin is safe in the amounts usually used rectally, but then went on to establish a 3 g suppository as the only adult dose and a 1 to 1.5 g suppository dosage range for children under 6 years of age. One comment stated that it is unclear whether the dosage refers to the total weight of the suppository or to the weight of glycerin in each suppository. The comments stated that marketed adult glycerin suppositories range from 2 to 3 g of glycerin per suppositories range from 1 to 1.7 g of glycerin per suppository. The comments recommended that the monograph should more closely reflect what has been marketed. One comment also noted that recommended § 334.12(a) made no specific mention of dosage levels for infants or for children 6 to 12 years of age. The comment suggested that the dosage be clarified by revising the Panel's final sentence in § 334.12(a) to read "Adults and children 6 years or older . . ." and by revising the second sentence to read "Infants and children under 6 years of age . . . ."

The agency agrees that the dosages for glycerin suppositories should be clarified and believes that the Panel's recommended dosages for glycerin suppository refer to the weight of the glycerin in each suppository. Based on the information provided by the comments and the agency's independent survey of marketed glycerin suppository products (Ref. 1 through 4), the agency has determined that most glycerin suppositories are manufactured and marketed according to "The United States Pharmacopeia" (USP) specifications, and that adult suppositories contain between 2 and 3 g of glycerin, and children's suppositories contain between 1 and 1.75 g of glycerin. The tentative final monograph reflects these ranges.

Also, the dosages recommended by the Panel in § 334.12(a) need to be revised to indicate that the adult dosage range is the same as for children 6 years of age and over. However, as discussed in part II paragraph 2. below, constipation in children under 2 years of age should be diagnosed by a doctor. Therefore, dosages for children under 2 years of age are included in the monograph only under professional labeling.

References

(1) Letter from M. K. Laboratories to Michael Kennedy, FDA, November 6, 1981, OTC Volume 09LTFM, Docket No. 78N-036L, Dockets Management Branch.

(2) Letter from E. R. Squibb and Son, Inc., to Michael Kennedy, FDA, October 23, 1981, OTC Volume 09LTFM, Docket No. 78N-036L, Dockets Management Branch.

(3) Letter from Suppositoria Laboratories to Michael Kennedy, FDA, October 26, 1981,

OTC Volume 09LTFM, Docket No. 78N-036L, Dockets Management Branch.

(4) Letter from E.R. Squibb and Son, Inc., to Michael Kennedy, FDA, February 3, 1982, OTC Volume 09LTFM, Docket No. 78N-036L, Dockets Management Branch.

46. One comment recommended that the warning for products containing glycerin in recommended § 334.54(a)(1), i.e., "For rectal use only and not for oral use. Large doses of glycerin if taken orally can lead to serious toxic effects," be shortened to "For rectal use only." The comment stated that this shortened statement plus the mandatory warning in § 330.1(g), "In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately," are sufficient to convey the full intent of the warning, and that the other statements are redundant.

The agency agrees with the comment and is proposing that the warning read "For rectal use only." Consumers are generally aware of the mode of administration of suppository dosage forms. The phrase "for rectal use only" is sufficient for those who are unfamiliar with this dosage form. While it is unlikely that these products would be ingested, the mandatory warning in § 330.1(g) (21 CFR 330.1(g)) about accidental ingestion informs consumers of the proper action to take in case of accidental ingestion.

E. Comments on Lubricant Laxatives

47. Two comments suggested that the first phrase of the caution for mineral oil in recommended § 334.56(a)(1), "to be taken only at bedtime," should be deleted because this information is already provided in the "Directions for use" in recommended § 334.14(a).

Three other comments disagreed with the wording of the dosage for mineral oil emulsion in recommended § 334.14(b) which states, "Adult oral dosage is 15 mL to 45 mL of mineral oil component of emulsion administered orally twice daily with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtimes . . . ." The comments argued that this dosage statement could be misinterpreted to mean that 15 to 45 mL should be taken twice daily, giving a maximum daily dose of 30 to 90 mL, although the Panel clearly meant 15 to 45 mL to be the maximum daily dose, to be taken in two equally divided doses. The comments also pointed out that the children's dosage statment in recommended § 334.14(b) could be similarly misinterpreted. One of the comments suggested that recommended § 344.14(b) be revised to read, "Adult oral dosage is 15 mL to 45 mL daily of mineral oil component of emulsion administered orally twice daily in divided doses with the first dose taken on arising and the second dose taken at bedtime and neither dose at mealtimes."

The agency agrees that the warnings, dosage, and directions for use for both mineral oil and mineral oil emulsion are confusing and require clarification. The difference in directions for use between mineral oil and mineral oil emulsion is not adequately justified. Mineral oil emulsion is merely a different formulation of mineral oil; mineral oil is the active ingredient in mineral oil emulsion. Therefore, this tentative final monograph provides for warnings and directions for use for mineral oil only. The emulsion formulation is not included in this tentative final monograph, although manufacturers may choose to formulate mineral oil as either the plain oil or as an emulsion. The directions for use will provide for a minimum adult dose of 15 mL with a total maximum daily dose of 45 mL. For children over 6 years of age, the minimum dose is 5 mL with a maximum total daily dose of 15 mL. Mineral oil is most often taken at bedtime, but restricting its administration to a particular time of day is unnecessary except that it should not be administered with meals because of potential interference with the absorption of fat-soluble vitamins. Because some persons prefer to take mineral oil in divided doses, the agency is proposing that directions for use provide that products may be labeled so that the dosage may be administered in either a single daily dose or in divided doses provided that no dose is taken at mealtimes. The agency believes that these directions more accurately reflect the current usage of mineral oil.

48. Two comments objected to the statement required for mineral oil products in recommended § 334.56(a)(1) that warns against the administration of mineral oil "to pregnant women, to bedridden or aged patients." The comments argued that the caution was unwarranted in view of the considerable body of evidence (Refs. 1 through 6) supporting the safe and effective use of mineral oil in such patients and in view of the general warning in recommended § 334.50(c)(3), which limits the OTC use of laxative products to 1 week. One of the comments argued that "since difficulties in absorbing vitamins A, D, E, and K occur very rarely and then only under conditions of chronic use of lubricant laxatives, the caution is not necessary because use is limited to 1 week."

The agency concludes that the studies submitted by the comments (Refs. 1 through 6) do not support deleting the statement in recommended § 334.56(a)(1) that warns against the use of mineral oil by pregnant women and bedridden patients. Only one of the submitted studies (Ref. 2) included pregnant women, and no mineral oil was administered in that study. Because data are lacking to support the comments' argument, the agency concurs with the Panel that lubricant laxatives should not be given to pregnant women. The Panel pointed out that ingested mineral oil may lower prothrombin levels, probably secondary to impaired vitamin K absorption, and therefore the regular use of mineral oil in pregnancy may predispose the newborn to hemorrhagic disease (40 FR 12912).

Additionally, only one of the submitted studies (Ref. 3) dealt extensively with bedridden patients, and, again, no mineral oil was administered. Because data are again lacking to support the comments' argument, the agency concurs with the Panel that lubricant laxatives should not be given to bedridden patients because the ingested mineral oil may be aspirated and cause lipid pneumonitis (40 FR 12912). In view of the lack of data, the agency does not believe that the 1-week limitation in recommended § 334.50(c)(3) would assure the safe use of mineral oil in pregnant women or bedridden patients.

The other submitted studies (Refs. 1, 4, 5, and 6) offer sufficient evidence to support the safe use of lubricant laxatives, such as mineral oil by aged patients. The Panel was primarily concerned that the absorption of a number of dietary nutrients, including fat-soluble vitamins, may be impaired by the ingestion of mineral oil during or after meals. Labeling that directs persons not to take mineral oil with meals can reduce the possibility of mineral oil interfering with the absorption of vitamins in aged patients. Also, the Panel's warning against the use of mineral oil by the aged apparently was based on a concern that aged patients have a debilitated or "worn out" gastrointestinal tract. The submitted studies, however, demonstrate that the gastrointestinal tract does not "wear out" with age and that clinical observation of gastrointestinal problems in older patients differs little from younger individuals (Refs. 1 and 6). Based on these data, the agency believes that a warning against the use of mineral oil laxatives by a particular group of adults because of their age is unwarranted without further sound medical rationale supporting specific age limitations. Therefore, the agency has deleted the

phrase "or aged" from the warning statement required for mineral oil products in this tentative final monograph.

In addition, in the Federal Register of December 3, 1982 (47 FR 54750), the agency published a final rule amending the general drug labeling provisions in Part 201 (21 CFR 201.63) to include a warning concerning the use by pregnant or nursing women of OTC drugs intended for systemic absorption. The final rule states that, where a specific warning relating to use during pregnancy or while nursing has been established for a particular drug product in an NDA or for a product covered by an OTC drug final monograph, the specific warning shall be used in place of the general warning, unless otherwise stated in the NDA or in the final OTC drug monograph. While the warning recommended by the Panel covers use of mineral oil during pregnancy, it does not refer to its use by nursing mothers. Therefore, the following additional statement is being proposed in this tentative final monograph for mineral oil: "As with any drug, if you are nursing a baby, seek the advice of a health professional before using this product." Accordingly, in this tentative final monograph the agency proposes that the specific pregnancy and nursing warnings discussed above for mineral oil supersede the general warning required under § 201.63.

References

(1) Mulinos, M.G., and A.J. Maloney, "Treatment of Constipation in the Aged," *The Journal of the Medical Society of New Jersey*, 66:619–622, 1969.

(2) Greenhalf, J.O., and H.S.D. Leonard, "Laxatives in the Treatment of Constipation Pregnant and Breast-Feeding Mothers," *The Practitioner*, 210:259–263, 1973.

(3) Tirsch, H.S., and S. Rosenfeld, "Correction of Constipation in Severely Incapacitated Invalids and in Patients with Neurologic Diseases," *American Journal of Gastroenterology*, 31:702–705, 1959.

(4) Montilla, E., "Treatment of Chronic Constipation with an Emulsion of Milk of Magnesia and Mineral Oil," *Clinical Medicine*, 73:75–77, 1966.

(5) Cohen, T., and L. Gitman, "Clinical Evaluation of the Gastrointestinal Tract in the Aged," *The American Journal of Gastroenterology*, 32:422–434, 1960.

(6) Magnuson, C., "The Geriatric and Bedridden Patient and the Large Bowel," *Nebraska State Medical Journal*, 50:73–78, 1965.

49. Two comments maintained that the statement recommended for mineral oil products in § 334.56(a)(1) that warns against giving mineral oil "to persons having recent episodes of vomiting or regurgitation, or to persons having abdominal pain" is redundant and duplicates the general warning for all laxatives in recommended § 334.50(c)(1), which states, "Do not use this product when abdominal pain, nausea, or vomiting are present." The comments suggested revising the warning to eliminate the statement concerning vomiting, regurgitation, and abdominal pain from the specific mineral oil warnings in recommended § 334.56.

The agency agrees with the comments. Accordingly, recommended § 334.56 has been revised to delete the phrase "to persons having recent episodes of vomiting or regurgitation, or to persons having abdominal pain."

50. One comment requested that the phrase "except on the advice of a physician" be added to the drug interaction precaution in recommended § 334.56(a)(2), i.e., "Do not take this product if you are presently taking a stool softener laxative."

The agency agrees with the comment that situations may exist in which a physician might choose to use or combine drugs for a medical reason. In other recent tentative final monographs the agency has adopted the phrase "unless directed by a doctor" in place of phrases such as "except on the advice of a physician." Accordingly, the drug interaction precaution in recommended § 334.56 has been revised in the tentative final monograph to read, "Do not take this product if you are presently taking a stool softener laxative unless directed by a doctor." The tentative final monograph also includes the option of using either the word "physician" or the word "doctor" in OTC laxative labeling.

F. Comments on Saline Laxatives

51. Two comments stated that the warning for saline laxatives in recommended § 334.58(a), which states, "For occasional use only. Serious side effects from prolonged use or overdosage may occur," is unnecessary and redundant. The comments pointed out that the general warning in recommended § 334.50(c)(3), which states, "This product should not be used for a period of longer than 1 week except under the advice and supervision of a physician," restricts the prolonged use of any laxative. One comment further noted that the Panel's statement at 40 FR 12910 that saline laxatives should be restricted to occasional use only, as serious electrolyte disturbances have been reported with their long-term or daily use, is not supported by any of the references cited by the Panel for saline laxatives. The comment submitted a reference claiming to show that there is no serious disturbances to the electrolytic balance in the blood with the use of a kit containing magnesium citrate (Ref. 1). The comments concluded that there was no clinical justification for singling out saline laxatives such as magnesium citrate for disturbing electrolyte balance and recommended that § 334.58(a) be deleted from the monograph.

The agency has reviewed the data cited by the comment and believes that they do not provide a basis for deleting the warning. Magnesium citrate was administered once to each patient as part of a bowel cleansing regimen in preparing patients for barium x-ray. Although none of the patients experienced any electrolyte disturbances, the data do not provide information regarding the Panel's concerns about electrolyte disturbances from long-term use of saline laxatives. However, the general warning recommended by the Panel in § 334.50(c)(3) restricts the use of any laxative to not longer than 1 week. Therefore, the specific warning in recommended § 334.58(a) is unnecessary and is not included in the tentative final monograph.

Reference

(1) Irwin, G. A. L., J. E. Shields, and W. W. Wolff, "Clearer Roentgenographic Visualization of the Colon," *Gastroenterology*, 67:47–50, 1974.

52. Two comments noted that recommended § 334.16(a)(2) states that magnesium citrate products may be formulated in combinations with the sequestering agents, citric acid and anhydrous sodium citrate, to allow magnesium to be held in solution as a complex. The comments pointed out that the monograph for magnesium citrate solution in "The National Formulary" lists potassium bicarbonate in the prime formula and provides for sodium bicarbonate as an alternate ingredient (Ref. 1). The comments proposed that recommended § 334.16(a)(2) be revised to permit the use of potassium citrate as an alternate ingredient to sodium citrate.

Since submission of the comment, magnesium citrate oral solution has been added as an official article to the USP (Ref. 2). The agency has no objection to the use of different sequestering agents for magnesium citrate formulations because these ingredients are not active ingredients and do not contribute to the laxative effect of the product. The agency points out that the OTC drug review is primarily an active, not inactive ingredient review. Inactive ingredients are not usually included in the OTC drug monographs. They must, however, meet the requirements of § 330.1(e) (21 CFR

330.1(e)) that they be suitable ingredients that are safe and do not interfere with the effectiveness of the product. Because the purpose of the OTC drug review process is to determine the safety and effectiveness of OTC drugs, the OTC advisory review panels occasionally made recommendations with respect to inactive ingredients; these recommendations were made to call attention to those inactive ingredients that could potentially interfere with the safety and effectiveness of the product. In the case of the inactive ingredients in magnesium citrate solution, the agency is unaware of any evidence to demonstrate that they could potentially interfere with the safety and effectiveness of the product. Therefore, the specific sequestering agents for magnesium citrate solution which had been recommended by the Panel are not included in the tentative final monograph.

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, pp. 389–390, 1975.

(2) "The United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 459–460, 1980.

53. Two comments submitted a number of studies (Refs. 1 through 4) to show that one of the major professional uses of magnesium citrate solution is for the preparation of the colon for x-ray and endoscopic examination. Based on these studies, the comments requested that recommended § 334.80 be ameded to allow the following professional labeling claims for magensium citrate: "For the preparation of the colon for x-ray and endoscopic examination." One comment further proposed that the claim "for use in preparation of the patient for surgery" also be allowed.

The agency has reviewed the submitted studies and believes there is sufficient evidence to support the use of magnesium citrate as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray or endoscopic examination. However, none of the studies used magnesium citrate solution alone to evacuate and cleanse the colon. In each of the studies, magnesium citrate solution was used with either bisacodyl, enemas, overhydration, or dietary restirctions as one part of an overall regimen in preparing the patients for surgery, or preparing the colon for x-ray or endoscopic examination.

Therefore, the agency is proposing in the tentative final monograph that the Category I professional labeling claim be limited to the following: "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray or endosopic examination."

The agency's comments and evaluation on the data are on file in the Dockets Management Branch (Refs. 5 and 6).

References

(1) Comment No. C00015, Docket No. 78N-036L, Dockets Management Branch

(2) Comment No. C00043, Docket No. 78N-036L, Dockets Management Branch.

(3) Sloan, R. D., et al., "What is the Best Way to Prepare the Colon for Radiological Study?" *Modern Medicine*, 38:198–201, 1970.

(4) Irwin, G. A. L., et al., "Clearer Roentgenorgraphic Visualization of the Colon," *Gastroenterology*, 67:47–50, 1974.

(5) Letter from William E. Gilbertson, FDA, to Richard Neimeth, National Magnesium Co., Coded ANS LET 012, Docket No. 78N-036L, Dockets Management Branch.

(6) Letter from William E. Gilbertson, FDA, to Warren L. Myers, Warren-Teed Pharmaceuticals Division of Adria Laboratories Inc., Coded ANS LET 011, Docket No. 78N-036L, Dockets Management Branch.

54. One comment requested that recommended § 334.16(b) be revised to include an infant dosage for milk of magnesia (magnesium hydroxide). The comment pointed out that an infant dosage for milk of megnesia was submitted to the Panel for evaluation, but that neither the Panel's minutes nor the preamble to the monograph reflect any consideration of this issue. Noting that its laxative product, which contains milk of magnesia and is labeled for use in infants, has been marketed for over 25 years, the comment argued that there is nothing in the medical literature that would cast doubt upon the continued use of an infant dosage for milk of magnesia.

Magnesium hydroxide has been used for the relief of constipation in infants. The available literature indicates that the magnesium hydroxide dosage generally recommended for infants is 0.035 to 0.043 gram per kilogram per dose (Refs. 1 and 2). However, as discussed in part II. paragraph 2. below, the agency believes that constipation in children under 2 years of age could be indicative of a more serious condition that should be diagnosed by a doctor. Therefore, dosages for children under 2 years of age are included in the tentative final monograph only under professional labeling.

References

(1) Fingl, E., "Laxatives and Cathartics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, The Macmillan Publishing Co., New York, p. 1005, 1980.

(2) Shirkey, H.C., editor, "Pediatric Therapy," 6th Ed., The C.V. Mosby Co., St. Louis, p. 1219, 1980.

55. Two comments noted that the daily dosage range for magnesium citrate as expressed in milliequivalents (mEq) magnesium ion is listed in the recommended monograph as 77 to 126 mEq magnesium ion in § 334.16(a) under Subpart B—Active Ingredients and as 77 to 141 mEq magnesium ion at 40 FR 12910. The comments conteded that both calculations for mEq magnesium ion were incorrect and noted that the mEq stated for the magnesium ion neither conformed to the volume limits of the usual daily dosage range for magnesium citrate solution, nor to the magnesium oxide limits, as listed in the monograph for magnesium citrate solution in the "National Formulary" (Ref. 1). The comments further contended that the upper limit of 18 g for the daily dosage range of magnesium citrate recommended in § 334.16(a) should be extended to 25 g because the usual daily dosage of magnesium citrate solution varies from 200 to 350 mL.

The agency agrees with the comments that the daily dosage range for magnesium citrate as expressed in mEq magnesium ion is in error. However, the agency does not believe that there is a need to state the dosage for administration in milliequivalents because such information could be confusing to consumers. The agency also agrees that the upper limit of the daily dosage range of magnesium citrate should be extended to 25 g. Based on submissions to the agency, products currently marketed, and other available information, the agency notes that magnesium citrate, when used as a laxative, is usually formulated and administered as an oral solution within the requirements of the USP. Magnesium citrate oral solution, (see comment 52 above) contains in each 100 mL, 5.8 to 7.1 g of magnesium citrate equivalent to not less than 1.55 g and not more than 1.9 g of magnesium oxide (Ref. 2). The usual daily dosage for magnesium citrate oral solution is 200 to 350 mL. Based on the lower and higher limits of the amount of magnesium citrate in 100 mL of solution, the usual daily dosage would contain 11.6 to 24.8 g of magnesium citrate. The agency is expanding the dosage range for magnesium citrate for use as a laxative from 11 to 18 g to 11 to 25 g to be compatible with the USP requirements. Therefore, the following directions for use are included in the tentative final monograph for magnesium citrate:

"Adults and children 12 years of age and over: oral dosage is 11 to 25 grams. [illegible]ldren 6 to under 12 years of age: oral [illegible] is 5.5 to 12.5 grams. Children 2 to under 6 years of age: oral dosage is 2.7 to 6.25 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor."

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, pp. 389–390, 1975.

(2) "The United States Pharmacopeia," 20th Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 459–460, 1980.

56. Four comments objected to the phrase "taken in dividend doses" in the total daily dosage for magnesium citrate in recommended § 334.16(a) and for magnesium hydroxide in recommended § 334.16(b). Several of the comments stated that the phrase "in divided doses" is not applicable to the administration of magnesium citrate and magnesium hydroxide because these laxative ingredients are usually administered in single doses, that is, "once daily or at bedtime, or as directed by a physician." One of the comments pointed out that magnesium citrate [illegible]tion is packaged in a single-dose [illegible]ontainer and each unit cannot be used more than once. Another comment stated that magnesium hydroxide when used as an antacid is given in divided doses, but when used as a laxative is given as a larger single dose. The comments pointed out that, in the absence of safety or effectiveness questions, there is no reason to prohibit [illegible] single-dose administration of these [illegible]gredients. Some of the comments [illegible]equested that the dosage regimen [illegible]ermit both single and divided dosage [illegible]irections. Others suggested a single [illegible]osage, once daily or at bedtime, or as [illegible]irected by a physician.

Magnesium salts, magnesium citrate, magnesium hydroxide, and magnesium sulfate when used as laxatives are generally administered as a single dose once per day (Refs. 1, 2, and 3). The agency is not aware of any evidence contradicting the safety or effectiveness of these laxative ingredients when the recommended total daily dosage is administered either in a single dose once per day or in divided doses. Therefore, the tentative final monograph provides for both single daily doses or divided doses of the magnesium salts.

F[illegible]

(1) [illegible], E., "Laxatives and Cathartics," *in* The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, The Macmillan Publishing Co., New York, p. 1005, 1980.

(2) Swinyard, E.A., "Gastrointestinal Drugs," *in* "Remington's Pharmaceutical Sciences," 16th Ed., edited by A. Osol et al., The Mack Publishing Co., Easton, PA, pp. 738 and 744, 1980.

(3) Aviado, D.M., "Krantz and Carr's Pharmacologic Principles of Medical Practice," 8th Ed., The Williams and Wilkins Co., Baltimore, p. 944, 1972.

57. Three comments requested a revision of recommended § 334.58(b), which provides for storage of magnesium citrate solution in a cold place (refrigerator temperature) to retard decomposition. The comments pointed out that this statement was appropriate for magnesium citrate solution prior to the modification of the manufacturing process in which a pasteurization step was introduced. The comments further pointed out that the requirements in the "National Formulary" for magnesium citrate solution call for storage at controlled room temperature or in a cool place (Ref. 1). Therefore, the comments requested that § 334.58(b) either be deleted or replaced with the storage statement in the "National Formulary".

Magnesium citrate in oral solution is an official article in the USP (Ref. 2). Therefore, the agency agrees that the storage conditions for magnesium citrate in oral solution should conform to the current official compendium, which requires storage at controlled room temperature or in a cool place. The USP defines "controlled room temperature" as between 59 and 86 °F (15 and 30 °C) and "cool place" as between 46 and 59 °F and (8 and 15 °C) (Ref. 2). Therefore, this tentative final monograph states that magnesium citrate when formulated in oral solution should be stored at temperatures between 46 and 86 °F (8 and 30 °C).

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, pp. 389–390, 1975.

(2) "The United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 8 and 459–460, 1980.

58. One comment submitted a number of references (Ref. 1) to show that the phosphate salts administered either orally or rectally are useful therapy for preparing the colon for x-ray, endoscopic examination, and for preparing the bowel for surgery. The comment requested that recommended § 334.80(a), which contains the professional labeling for products containing phosphate salts, be amended to allow the claim "For use in preparation of the patient for surgery or for preparation of the colon for x-ray and endoscopic examination." In addition, the comment requested that the upper limits for the daily dosage range for orally administered sodium biphosphate and sodium phosphate in recommended § 334.16(d) be expanded from 19.2 g to 21.3 g for sodium biphosphate and from 7.2 g to 8 g for sodium phosphate for these professional labeling indications.

The agency reviewed the submitted studies and agrees with the comment that phosphate salts are useful therapy for use in preparation of the colon for x-day and endoscopic examination or for the preparation of the patient for surgery. However, in most of the submitted studies phosphate salts were not used alone, but were used as part of an overall bowel cleansing regimen, which included overhydration, dietary restrictions, and/or other laxative agents. Accordingly, the professional labeling section of the monograph for phosphate salts, has been amended to include the following indication: "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray or endoscopic examination." Also, the studies submitted did not contain sufficient data to justify an increase in the upper limit of the dosage ranges for sodium phosphate and sodium biophosphate. However, in this tentative final monograph the agency is expanding the dosage ranges for phosphate salts to be compatible with the USP as follows: (1) *Sodium phosphate/sodium biophosphate solution. Oral dosage.* Adults and children 12 years of age and over: oral dosage is sodium phoshpate 3.42 to 7.56 grams, and sodium biphosphate 9.1 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is sodium phosphate 1.71 to 3.78 grams and sodium biphosphate 4.5 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: Oral dosage is sodium phosphate 0.86 to 1.89 grams and sodium biphosphate 2.2 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor. *Enema dosage.* Adults and children 12 years of age and over: enema dosage is sodium phosphate 6.84 to 7.56 grams and sodium biphosphate 18.24 to 20.16 grams in a single daily dose. Children 2 to under 12 years of age: enema dosage is sodium phosphate 3.42 to 3.78 grams and sodium biphosphate 9.12 to 10.08 grams in a single daily dose. Children under 2 years of age; consult a doctor.

(2) *Sodium phosphate.* Adults and children 12 years of age and over: oral dosage is 3.42 to 7.56 grams in a single

daily dose. Children 10 to under 12 years of age: oral dosage is 1.71 to 3.78 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is 0.86 to 1.89 grams in a single daily dose. Children under 5 years of age: consult a doctor.

(3) *Sodium biphosphate.* Adults and children 12 years of age and over: oral dosage is 4.5 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is 2.25 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is 1.12 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor.

The agency's comments and evaluation on the data and its recommendations are on file in the Dockets Management Branch (Ref. 2).

References

(1) Comment Nos. C00002 and C00022, Docket No. 78N-036L, Dockets Management Branch.

(2) Letter from William E. Gilbertson, FDA, to Fred T. Wickis, C. B. Fleet Co., ANS LET 008, Docket No. 78N-036L, Dockets Management Branch.

59. One comment stated that the usual daily dosages recommended for the phosphate salts (disodium phosphate, sodium phosphate, sodium biphosphate, and monosodium phosphate) as stated in the table at 40 FR 12911 and in recommended § 334.16(d) are unclear because disodium phosphate and monosodium phosphate are synonyms for sodium phosphate USP and sodium biphosphate USP, respectively. The comment recommended that the names monosodium phosphate and disodium phosphate, along with their corresponding dosages, be deleted. The comment suggested that the monograph state that only the USP names, with the designated chemical formulas and molecular weights for sodium phosphate and sodium biphosphate, be allowed in all labeling to avoid error in interpreting which salt is meant. Another comment stated that the milliequivalents expressed for the ionization products of the phosphate salts should have been calculated for the products resulting from ionization in aqueous solution, as would be ingested by the consumer, rather than the phosphate ion species released by alkaline degradation.

The agency agrees with the comment that the names and the dosages for the phosphate salts as stated at 40 FR 12911 and in recommended § 334.16(d) and § 334.35(a) are confusing. Disodium phosphate and monosodium phosphate are synonyms for sodium phosphate and sodium biphosphate, respectively. However, only the official names of these ingredients, i.e., sodium phosphate and sodium biphosphate, need to be designated in the monograph. Also, because these ingedients are official compendial articles there is no need to specify their molecular weight and chemical formula in the monograph.

Although the agency agrees with the comment that the milliequivalents expressed for the ionization of phosphate salts should have been calculated for the products existing in aqueous solution, in this tentative final monograph the agency states the dosage in grams of sodium phosphate and sodium biphosphate. (See comment 58 above.)

60. One comment submitted an unpublished study in response to the Panel's recommendations at 40 FR 12919 for further definitive, well-designed studies to establish a safe and effective laxative dose for tartaric acid and tartrate preparations (Ref. 1). The comment stated that the study supports the safety of tartaric acid and tartrate preparations and supports reclassifying them from Category III to Category I for use as a laxative.

The Panel recommended that the usual daily dose of tartrate preparations when used as laxatives (5 to 10 g) was probably safe, but that additional data were necessary to justify an increase in the total daily dose beyond 10 g. The submitted study was designed to determine the extent of absorption and metabolism of sodium ^{14}C-tartrate in the rat and in humans and to study quantitatively the effect of tartrate ingestion upon the acid-base status in humans. From the results in one phase of the study, consisting of the administration of sodium ^{14}C-*DL*-tartrate orally and parenterally to humans and rats, intestinal absorption was calculated as 18 percent of the dose in humans and 81 percent in rats, of which the greater portion in both humans (14 percent) and rats (70 percent) was excreted in the urine. Because the ^{14}C-labeled tartrate was excreted as respiratory carbon dioxide to a greater extent after oral than parenteral administration, the authors concluded that the main site of tartrate metabolism is in the intestine. Studies measuring tartrate metabolism and carbon dioxide liberation from intestinal bacteria confirmed this conclusion. In the acid-base studies, one subject was given 24 g and another 30 g per day of unlabeled sodium *L*-tartrate. The authors found no evidence of renal toxicity in the two subjects as assessed by maintenance of normal creatinine clearance and the absence of proteinuria. However, the authors indicated, based on the weight of the stools collected, that the laxative effect was slight and questioned the reputation of the tartrates as laxatives.

Although the study provides information to establish the safety of tartrate preparations in the dosages normally used in OTC laxative formulations, additional effectiveness data are needed before tartaric acid and tartrate preparations can be generally recognized as effective for oral use as OTC laxatives.

The agency's comments and evaluation on the data and its recommendation for additional studies are on file in the Dockets Management Branch (Ref. 2).

References

(1) Wrong, O. M., et al., "The Metabolism of Tartrate in Man and the Rat," draft of unpublished paper, Comment No. C0079, Docket No. 78N-036L, Dockets Management Branch.

(2) Letter from William E. Gilbertson, FDA, to Bernard Misek, Beecham Products, coded ANS C0082, Docket No. 78N-036L, Dockets Management Branch.

G. Comments on Stimulant Laxatives

61. One comment stated that there was ambiguity in the Panel's definition of "stimulant laxative" in recommended § 334.3(l), which states, "An agent that promotes bowel movement by one of more direct actions on the intestine," because this definition could conceivably be interpreted to include every clinically active laxative agent. According to the comment, saline and hyperosmotic laxatives would be included within the definition because they act directly on the intestine by increasing intestinal water content, thereby promoting bowel movement; bulk laxatives would be included because they increase motor activity of the colon through pressure stimulation by increasing intestinal bulk and water content. The lubricant laxatives would also be included because they exert one of more direct actions on the intestine by coating the intestinal wall to lubricate the passage of the intestinal contents. The comment recommended that stimulant laxative be defined as "an agent that promotes bowel movement by increasing peristalsis in the colon through direct stimulation of neuro-muscular components of the intestinal wall." The comment concluded that this definition does not include saline and hyperosmotic laxatives which do not increase peristaltic activity by direct neuro-muscular stimulation of the colon, but act through an intervening pharmacologic mechanism. Another comment stated that stimulant laxatives

do not "stimulate" anything, but act in the same manner as the other laxatives.

[redacted]ining stimulant laxative, the [redacted]ovided a general definition that it felt would be applicable to all stimulant laxatives. The panel recognized that some of the so-called "stimulant laxatives" have recently been shown to promote laxation by means other than stimulation, but the exact mechanism by which they promote laxation is not known (40 FR 12906). Until the precise mechanisms for the "stimulant laxatives" have been defined, there is sound basis for changing the Panel's definition.

62. One comment disagreed with the Panel's recommendation that all stimulant laxatives bear the class warnings in recommended § 334.60(a) (1), (2), and (3). The comment argued that the ingredients classified as stimulant laxatives are markedly different from one another in terms of chemical composition, clinical pharmacology, and site of intestinal action. These differences result in wide variations in therapeutic response and clinical toxicity for the individual ingredients. The comment recommended amending the warnings and caution statements so that they properly reflect the clinical use experience reported for h ingredient, rather than have class ..arnings for the stimulant laxatives.

The agency agrees with the comment. The class warnings for stimulant laxatives contained in recommended § 334.60(a) (1), (2), and (3) are not included in this tentative final monograph. (See comments 63, 64, and 65 below.) The agency believes that the general warnings for OTC drugs in § 330.1(g) (21 CFR 330.1(g)), the general OTC laxative warnings in recommended § 334.50(c), and the ingredient-specific warnings for bisacodyl, castor oil, and phenolphthalein, will provide consumers with adequate warnings for the use of stimulant laxatives. The specific warnings are based on each ingredient's specific clinical pharmacology, clinical toxicity, and therapeutic response. Thus, as recommended by the comment, the warnings for the stimulant laxatives in the tentative final monograph are now limited to ingredient-specific warnings.

63. Numberous comments objected to the Panel's recommended warning for stimulant laxatives in § 334.60(a)(1), which states, "Caution: Prolonged or continued use of this product can lead to laxative dependency and loss of normal bowel function." They also objected to the following portion of the warning in [redacted]mended § 334.60(a)(2): "Serious side effects from prolonged use . . . can occur." Some of the comments argued that these warnings were unnecessary because the general warning for all OTC laxative drugs in recommended § 334.50(c)(3) already warns that OTC laxatives should not be used longer than 1 week excpet under the advice and supervision of a physician. Therefore, according to the comments, concerns about serious side effects, loss of normal bowel function, and laxative dependency from prolonged use are not an issue. Several of the comments argued that because the Panel could not define the term "dependency" (in recommended § 334.60(a)(1)), the warning should be deleted. Other comments argued that the warnings should not apply to specific stimulant laxatives. One comment cited 23 references (Ref. 1) in support of its argument that prolonged use of standardized senna during clinical studies did not cause serious side effects or lead to laxative dependency. One of the references, an article by Abraham (Ref. 2), describes a method for treating chronic constipation through the prolonged use of seena with gradually reduced doses given until regular bowel rhythm has been established and the need for a laxative is eliminated. The comment argued that this demonstrates that senna does not cause "dependency." Another comment cited an article by Dreiling, Fischl, and Fernandez (Ref. 3) in support of its contention that the prolonged use of bisacodyl does not cause serious side effects. The article reported a clinical trail in which bisacodyl was given for as long as 24 weeks and in doses as high as 20 mg per day without causing serious side effects "from prolonged use." The comments all recommended that § 334.60(a)(1) and the portion of § 334.60(a)(2) that concerns prolonged use, be deleted from the monograph.

The agency agrees with the comments that the warnings regarding prolonged use should be deleted from the monograph. The warning in recommended § 334.50(c)(3), which limits the use of laxative products to not longer than 1 week, is sufficient to warn consumers against the prolonged use of OTC laxatives. The agency has also reviewed the references cited by the comments and believes that standardized senna concentrate and bisacodyl used under professional supervision do not cause serious side effects from prolonged use or lead to laxative dependency. Thus, the warning in recommended § 334.60(a)(1), and that portion of the warning in recommended § 334.60(a)(2) concerning prolonged use, do not appear warranted for stimulant laxatives as a group and are not included in this tentative final monograph.

Reference

(1) Comment No. 37, Docket No. 78N-036L, Dockets Management Branch.

(2) Abrahams, A., "A Re-educative Regimen for Chronic (functional) Constipation," *The British Journal of Clinical Practice*, 18:1-5, 1964.

(3) Dreiling, D. A., R. A. Fischl, and O. Fernandez, "The Therapeutic Usefulness of Dulcolax (Bisacodyl), A New Nonpurgative Laxative," *American Journal of Digestive Disease*, 4:311-320, 1959.

64. Several comments objected to the portion of the warning in recommended § 334.60(a)(2) for stimulant laxatives which states that "Serious side effects from . . . overdose can occur." The comments recommended deleting this portion of the warning because it is repetitious of the general overdose warning for OTC drugs in § 330.1(g) which states, "In case of accidental overdosage, seek professional assistance or contact a poison control center immediately."

The agency agrees with the comments. Therefore, that portion of recommended § 334.60(a)(2) concerning overdose is not included in this tentative final monograph. In addition, the remainder of the warning in recommended § 334.60(a)(2) concerning prolonged use is also not included in this tentative final monograph. (See comment 63 above.)

65. Several comments argued that the Panel's recommended warning in § 334.60(a)(3) which states, "This product should be used only occasionally, but in any event no longer than daily for 1 week, except on the advice of a physician," is unnecessary. The comments pointed out that the warning in § 334.60(a)(3) is nearly identical to the general warning for all laxative drugs in recommended § 334.50(c)(3), which states "This product should not be used for a period of longer than 1 week except under the advice and supervision of a physician." The comments stated that the warning in § 334.60(a)(3) is repetitious and, therefore, should be deleted.

The agency agrees that the warnings in recommended §§ 334.60(a)(3) and 334.50(c)(3) provide similar information. To eliminate such redundancy, recommended § 334.60(a)(3) is not included in this tentative final monograph.

66. A comment asked whether danthron acts on the mucosa or the intramural nerve plexi and whether there is any possibility of nerve damage.

Although the precise mechanism of action of danthron is not known, the Panel discussed both theories of action—direct irritant effect on the

mucosa and stimulation of intramural nerve plexi. The Panel noted, however, that both theories lacked experimental confirmation. The agency is unaware of any data supporting the possibility of nerve damage when danthron is used as recommended for OTC use for no longer than 1 week.

67. One comment pointed out that the dosage statement for danthron in recommended § 334.18(e) does not contain a pediatric dosage and that the usual pediatric dosage for anthraquinone-type stimulant laxatives, such as danthron, is one-half the adult dosage for children 6 to 12 years of age and one-fourth the adult dosage for children 1 to 6 years of age. The comment recommended that the monograph be revised to include the following pediatric dosages for danthron:

Children 6 to 12 years of age: 37.5 mg daily
Children 1 to 6 years of age: 9.4 to 37.5 mg daily

The usual pediatric dosages that the comment recommends for danthron are limited to the senna-type anthraquinones. According to Godding (Refs. 1 and 2), Ewe (Ref. 3), Thompson (Ref. 4), and Breimer and Baars (Ref. 5), danthron differs from the senna-type anthraquinones in that the active components of the senna-type anthraquinones are rhein-glycosides containing a glucose molecule which "protects" the active components from systemic absorption. Thus the active components are not released from the glucose until they reach their active site in the colon. The active components of danthron, however, are "free anthraquinones," which lack the glucose molecule and are substantially absorbed systemically before reaching their active site in the colon. Because a considerable amount of danthron is absorbed before reaching its site of activity, it is less effective than the senna-type anthraquinones at a given dose. Also, because it is more readily absorbed into the system than the senna-type anthraquinones, danthron may be more systemically toxic. Therefore, the proportionate doses that apply to the senna-type anthraquinones cannot be applied to pediatric doses of danthron without scientific data to support the safety and effectiveness of a specific pediatric dose. The comment did not provide such data.

References

(1) Godding, E. W., "Hazards of Multilaxative Mixtures," *British Medical Journal*, 1:838, 1976.

(2) Godding, E. W., "Therapeutics of Laxative Agents with Special Reference to the Anthraquinones," *Pharmacology*, 14(Supplement 1):78–101, 1976.

(3) Ewe, K., "The Physiological Basis of Laxative Action," *Pharmacology*, 20(Supplement 1):2–20, 1980.

(4) Thompson, W. G., "Laxatives: Clinical Pharmacology and Rational Use," *Drugs*, 19:49–58, 1980.

(5) Breimer, D. D., and A. J. Baars, "Pharmacokinetics and Metabolism of Anthraquinone Laxatives," *Pharmacology*, 14(Supplement 1):30–47, 1976.

68. One comment pointed out that the professional labeling "for preparing the colon for x-ray or endoscopic examination" is provided for some of the anthraquinones, but not for danthron. The comment requested that this indication also apply to products containing danthron. No data were submitted to support this request.

The senna-type anthroaquinones are the only anthraquinone ingredients that contain professional labeling. As pointed out in comment 67 above, danthron reportedly is less effective than senna at a given dose because its active components are substantially absorbed into the system before reaching the active site in the colon. The active components of the senna-type anthraquinones appear to be "protected" from systemic absorption through their molecular structure which includes a glucose molescule. Data demonstrating that danthron is effective for use in "preparing of the colon for x-ray or endoscopic examination" are necessary before the agency can include this professional indication for danthron in the monograph. The comment did not provide any data; therefore, this indication is not included in this tentative final monograph.

69. Objecting to the classification of senna as a stimulant laxative, one comment argued that recent methods of investigation, described by Jones and Godding (Ref. 1), indicate that laxation resulting from senna is accompanied by the absence of interaluminal pressure and the rapid transport of colonic contents which, according to the comment, is almost the reverse action of stimulation. The comment stated that the Panel insisted on classifying senna as a "stimulant" as a matter of convenience. The comment contended that, although the exact mechanism of action for senna may not be known, the ingredient should not be classified "as a matter of convenience," but on the basis of scientific information.

The Panel reviewed the text cited by the comment (40 FR 12909) and considered the mechanism of action for senna discussed by the comment. The Panel pointed out that these mechanisms lack experimental confirmation. The comment provided no new data to show that these mechanisms are now accepted as scientifically sound.

Chemically, senna is identified as an anthraquinone as are the other "stimulant" laxatives such as cascara sagrada, danthron, etc. The major active components of the anthraquinone laxatives are anthraquinone glycosides (Ref. 2). Although the properties of the individual anthraquinone laxatives vary with the precise type of glycoside present and the ease with which the glycosides are released from the original molecule (Ref. 3), they are chemically related. Because this chemical relationship is known and the precise mechanism of action is unknown, the agency believes that there is little justification for abandoning the traditional "stimulant" classification as used by the Panel.

References

(1) "Management of Constipation," edited by Jones, F. A., and E. W. Godding, Blackwell Scientific Publications, London, p. 106, 1972.

(2) Godding, E. W. "Therapeutics of Laxative Agents with Special Reference to the Anthraquinones," *Pharmacology*, 14 (Supplement 1):78–101, 1976.

(3) Fingl, E., "Laxatives and Cathartics," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The Macmillan Co., New York, p. 977, 1975.

70. Serveral comments questioned the Panel's recommended dosages for senna preparations in § 334.18(h). The comment pointed out that 1 mL senna fluid extract is prepared from 1 g of senna leaf powder and requested that the dose for senna fluid extract be expanded from the 2 mL dose recommended by the Panel to 0.5 to 2 mL to correspond to the recommended dose for senna leaf powder (40 FR 12909). The comment also stated that senna syrup is prepared from a 1 to 4 dilution of senna fluid extract; therefore, the dose for senna syrup should be four times that allowed for senna fluid extract. The comment requested expanding the dosage for senna syrup from the 8 mL dose recommended by the Panel to provide for a range of 2 to 8 mL. The comment also stated that the parenthetical phrase "(single dose)" following the heading "Senna Preparations" in the Panel's anthraquinone dosage table at 40 FR 12909 was confusing and should be clarified. Another comment pointed out that the Panel did not provide for a rectal dose of senna, even though data on a suppository containing senna pod concentrate were submitted to the Panel. The comment requested that the

agency provide for a suppository dosage form in the monograph, with an adult dose of 0.6 to 1 g once or twice daily and dose for children over 60 pounds that one-half the adult dose.

The agency agrees that the Panel's recommended dosages for senna preparations are confusing and require clarification. The available data, including the submissions made to the Panel as well as additional references (Refs. 1 through 16), show that it is generally accepted that the active constituent in the various senna preparations is sennosides A and B. In many of the submissions to the Panel, the dose of the various senna preparations was standardized to the sennosides A and B content. Because the active constituent in the senna compounds is sennosides A and B, the agency is providing in the tentative final monograph a dosage for sennosides A and B only. The allowable sources of sennosides A and B, i.e., senna, senna pod concentrate, and senna fruit extract, are listed in the tentative final monograph, but specific dosages for each individual preparation (e.g., senna syrup, senna fluid extract, etc.,) are not provided as the Panel had recommended. Manufacturers may market their products in the formulation of their choice using any of the allowable sources of senna provided that the equivalent dosage conforms to the sennosides A and B dosage provided in the tentative final monograph.

In determining the dose of sennosides A and B to be included in the monograph, the agency found a wide variation in the single oral dose of the marketed products, from 12 mg up to 180 mg equivalent sennosides A and B. The single dose for most of the products ranged from 12 to 50 mg equivalent sennosides A and B with the provision of a repeat dose later in the day, resulting in a maximum total daily dose of 100 mg equivalent A and B. The dose for children 6 to 12 years of age was one-half the adult dose and for children 2 to 6 years of age the dose was one-quarter the adult dose. Because most of the marketed senna products fall within the above dosage schedule, the tentative final monograph reflects this dosage schedule:

The agency is aware of one product with a single adult dose of 160 mg equivalent sennosides A and B. However, this higher dose is not intended for general laxative purposes; it is used to cleanse te colon for x-ray or endoscopic examination. Although the agency believes this higher dose product may remain OTC, it is proposing that the indication be limited to the following: "For use as part of a bowel cleansing regimen in preparing the colon for x-ray or endoscopic examination." In addition, in the tentative final monograph the agency is proposing the following warning for these products in lieu of the general warnings in recommended § 334.50(c) (1) through (4): "Do not use this product unless directed by a doctor."

The agency has reviewed the data submitted on the suppository dosage form of senna containing 652 mg senna pod concentrate (equivalent to 30 mg sennosides A and B) and concludes that it is sufficient to establish general recognition of safety and effectiveness as an OTC laxative. Thirteen studies in 2,289 patients were presented to support the safety and effectiveness of this preparation. In 11 studies the senna suppositories were used alone, and in the other 2 studies they were used as part of a bowel cleansing regimen in preparing the bowel for sigmoidoscopy. The suppositories were usually inserted once or twice daily. The suppositories were shown to be effective in approximately 90 percent of the patients. Based on these data the agency has included in the tentative final monograph a suppository dosage form of 30 mg sennosides A and B to be used once or twice daily. Because none of the submitted studies were conducted in children, a children's dose is not included in the monograph at this time.

References

(1) OTC Volume 090029.
(2) OTC Volume 090058.
(3) OTC Volume 090064.
(4) OTC Volume 090077.
(5) OTC Volume 090078.
(6) OTC Volume 090080.
(7) OTC Volume 090081.
(8) OTC Volume 090082.
(9) OTC Volume 090083.
(10) OTC Volume 090084.
(11) OTC Volume 090085.
(12) OTC Volume 090086.
(13) OTC Volume 090087.
(14) OTC Volume 090088.
(15) "The Anthraquinone Laxatives," Proceedings of a Symposium, *Pharmacology*, 14 (Supplement 1):1–108, 1976.
(16) "Natural Anthraquinone Drugs," Proceedings of the 2nd Symposium on the Anthraquinone Laxatives, *Pharmacology*, 20 (Supplement 1):1–134, 1980.

71. One comment suggested that the adult oral dosage of cascara sagrada extract of 200 mg to 400 mg daily in recommended § 334.18(c)(4) be changed to permit a lower limit of 100 mg to conform with the dosage stated in the "British Pharmacopeia".

The comment did not submit any data to establish that 100 mg is an effective dose for cascara sagrada extract, nor does the "British Pharmacopeia" contain such data. Cascara sagrada extract was recognized in an official United States compendium (Ref. 1) at the time of the Panel's review, and the usual oral dosage was stated as 300 mg. The Panel expanded this dosage to permit a wider range of 200 to 400 mg based on the data it reviewed. The current official United States compendia do not state a usual dosage for cascara sagrada extract. Therefore, in the absence of additional data demonstrating that a dosage of 100 mg of cascara sagrada extract is effective, the dosage is not revised in the tentative final monograph.

Reference

(1) "The National Formulary", 14th Ed., American Pharmaceutical Association, Washington, p. 123, 1975.

72. One comment suggested that the phrase "or adjust to individual requirements" be added to the required dosage statements for senna. The comment stated that consumers should be allowed to adjust the dosage because variations in laxative responses from person to person and in the same person at different times are well known. The comment pointed out that the Panel recognized that the smallest dose of a laxative that is effective is the optimal dose to use (40 FR 12905) and that Jones and Godding (Ref. 1) recognized that sublaxative doses of senna pod give symptomatic relief from colonic pain. The comment concluded that, although a dosage range is given for some senna ingredients, individuals should be given latitude to adjust their own particular dose, even if it does not fall within the limits set by the Panel.

The dosage ranges and single doses provided in the monograph for senna ingredients are the minimum effective dose and the maximum safe dose for most consumers. This determination is based on a review of the scientific data, including the text cited by the comment, and marketing experience for the ingredients. A dose lower than that provided in the monograph may produce a laxative effective in some individuals and a dose above the maximum may be safe in some individuals. For most consumers, however, decreasing the dose below the minimum effective level may not result in effective laxation, and increasing the dose above the maximum safe dose may result in the consumer's ingesting more drug than is necessary to achieve laxation, thus creating a risk of side effects.

The labeling of senna products will contain directions for use that reflect a safe and effective dosage. The dosage range for senna already takes into

account the varying requirements of some individuals and reflects safe and effective upper and lower limits for a majority of consumers. Therefore, the agency does not believe that the phrase "or adjust to individual requirements" is necessary in the labeling.

Reference

(1) "Management of Constipation," edited by F. A. Jones and E. W. Godding, Blackwell Scientific Publications, London, p. 42, 1972.

73. One comment disagreed with the Panel's recommended oral dosage and directions for bisacodyl. The comment requested that the dose of 5 to 15 mg in recommended § 334.18(b) be followed by the phrase "(usually 10 mg) * * * ", which, according to the comment, is the labeled does on a currently marketed bisacodyl product and which is supported by the bulk of the existing clinical data. In further, support, the comment contended that an article by Wolcott (Ref. 1) reported that a dose of 5 mg of bisacodyl caused cramping and failed to produce an adequate laxative effect in some patients. One comment disagreed with the Panel's recommended directions for taking bisacodyl at bedtime. The comment contended that there is no clinically valid reason for such a restriction and that for some consumers, e.g., housewives, it may be more convenient to take bisacodyl in the morning. The comment recommended revising § 334.18(b) accordingly.

Although bisacodyl is most often used in a dose of 10 mg, there is no reason to add "(usually 10 mg)" to the dosage information contained in the monograph. The Panel reviewed data that supports the safety and effectiveness of the 5 to 15 mg dosage range, and the agency agrees with the Panel's recommendation.

The agency believes the comment has misunderstood the article by Wolcott (Ref. 1). Wolcott reported that only 25 of 150 patients required a dose of bisacodyl greater than 5 mg while only a "few of the patents experienced moderate cramping." Further, Wolcott studied chronically ill patients with severe elimination problems, and such patients do not represent a population who would normally take an OTC laxative drug product without professional supervision.

The agency agrees that there is no clinically valid reason for restricting the use of bisacodyl to any particular time of day and is not including any such reference in the tentative final monograph. Also, information on the labeling regarding expected time of action (see comment 23 above) will provide consumers with sufficient information to choose the time of day for taking bisacodyl that is best suited to their schedule.

Reference

(1) Wolcott, L.E., "Laxation in Patients with Cronic Disease Utilizing Bisacodyl," *Archives of Physical Medicine and Rehabilitation*, 44:375–377, 1963.

74. One comment suggested several revisions in the Panel's recommended warnings for bisacodyl in § 334.60(b). The comment pointed out that there are two dosage forms of bisacodyl, a rectal suppository and an oral enteric-coated tablet, and that some warnings apply only to the enteric-coated tablet and not the suppository. The comment recommended placing these warnings under a section specifically intended for bisacodyl enteric-coated tablets. One comment stated that the warning in recommended § 334.60(b)(2), which warns against the use of bisacodyl enteric-coated tablets in children under 3 years of age, should be revised to warn against use in children under 6 years of age except under the supervision of a doctor because many children between 3 and 6 years of age are not able to swallow an enteric-coated tablet without chewing it. The comment also pointed out that in the recommended warning in § 334.60(b)(4), "This product may cause abdominal discomfort, faintness, rectal burning, and mild cramps," "rectal burning" applies only to the suppository. The comment suggested including the complete warning for the bisacodyl suppository only and deleting the phrase "rectal burning" for the enteric-coated tablet.

The agency agrees with the comment. In the tentative final monograph the warnings are separated into one section for the enteric-coated tablets and another for the suppository. The tentative final monograph is also revised to warn against the use of bisacodyl enteric-coated tablets in children under 6 years of age, unless directed by a doctor, because children between 3 and 6 years of age may have difficulty swallowing the enteric-coated tablet without chewing it. These tablets should not be chewed because gastric irritation may occur if the enteric coated is destroyed (Ref. 1).

Reference

(1) Fingl, E., "Laxatives and Cathartics," *in* "The Pharmacological Basis of Therapeutics", 5th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, pp. 976–986, 1975.

75. One comment questioned the following language in recommended § 334.60(b)(5) for products containing bisacodyl: "Store in a cool place at temperatures not above 86 °F (30 °C)." The comment pointed out that FDA has long recognized the USP definition of "cool" as any temperature between 46 and 59 °F (8 and 15 °C). The comment stated that FDA should continue to use this definition and should delete the word "cool" from the statement in § 334.60(b)(5). The comment also suggested that the Centigrade equivalent required in this statement be optional because few people in the United States relate exclusively to Centigrade temperatures. The comment recommended revising § 334.60(b)(5) to read, "Store at temperatures not greater than 86 °F."

The agency agrees that in view of the USP definition of the word "cool" (Ref. 1), the word "cool" should be deleted from the statement in § 334.60(b)(5), but disagrees that the Centigrade equivalent should be optional in this statement. The agency, however, will depart from the USP format of using only Centigrade temperature by also requiring the Fahrenheit temperature to be stated, because consumers are more familiar with Fahrenheit temperatures. In the tentative final monograph the agency is revising this statement to read as follows: "Store at temperatures not above 86 °F (30 °C)."

Reference

(1) "The United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 8, 1980.

76. One comment requested that the professional labeling for bisacodyl in recommended § 334.80(f) be expanded to include its use in postoperative care, in colostomies, for chronic constipation and bowel retraining, in antepartum care, in preparation for delivery, and in postpartum care. The comment submitted date (Ref. 1) which, it claimed, demonstrates the safety and effectiveness of bisacodyl for these professional uses.

Based on its evaluation of the data submitted and the National Academy of Science/National Research Council's (NAS/NRC) drug efficacy study reports for bisacodyl, published in the Federal Register of May 24, 1972 (37 FR 10521), the agency tentatively concludes the following:

Postoperative care, antepartum care, preparation for delivery, and postpartum care are simply specific professional use indications for an effective laxative. As such, they are acceptable for bisacodyl professional labeling. The NAS/NRC reached the same conclusion with respect to these claims.

The data do not support the professional use of bisacodyl in colostomy care. In this regard, only one study (Ref. 2) was submitted. The study suggests that less irrigation was required with bisacodyl, but the study was conducted using an oral solution of bisacodyl rather than the currently marketed dosage forms of tablets and suppositories. In addition, the presentation of the data is rudimentary and the data are too seriously deficient in detail to permit a complete evaluation. This study was also reviewed by the NAS/NRC and found less than convincing.

The data do not support a claim for the use of bisacodyl in chronic constipation. The NAS/NRC appeared to consider bisacodyl effective for chronic constipation but felt that the full range of possible toxic effects from long continued use was not fully known. A study by Mandel and Silinsky (Ref. 3) showed bisacodyl more effective than glycerin suppositories in a group of elderly and chronically constipated people but did not address the question of chronic use of bisacodyl. Two additional studies (Refs. 4 and 5) tend to support the initial effectiveness of bisacodyl in chronic constipation; however, the data are insufficiently characterized to provide strong support for this claim. In two other studies (Refs. 6 and 7), the data are too seriously deficient in detail to permit any detailed evaluation. The remaining study (Ref. 8) is irrelevant because it compares only single doses of several agents. No study assesses the chronic (continued) use of bisacodyl in chronic constipation. As such, additional data are necessary before a professional use claim of chronic constipation may be made for bisacodyl.

The data do not support the professional use of bisacodyl in bowel retraining. The NAS/NRC appeared to consider bisacodyl effective for bowel retraining but felt that the full range of possible toxic effects from long continued use was not fully known. Four studies were submitted in support of the bowel retraining claim (Refs. 9 through 12). The studies submitted were generally open studies, which offered minimal to no data, or merely provided the opinion of the investigator. Essentially the studies provided no evidence to indicate the usefulness of bisacodyl in a program of bowel retraining.

The agency's comments and observations on the data and its recommendation for additional studies are on file in the Dockets Management Branch (Ref. 13).

References

(1) Comment No. C0041 and Amendment 002, Docket No. 78N-036L, Dockets Management Branch.

(2) Stevenson, T.B., and J.C. Hawk, "Use of a Contact Laxative Solution (Dulcolax) as an Adjunct in Colostomy Control," *American Surgeon*, 30:118-122, 1964.

(3) Mandel, L., and J. Silinsky, "Bisacodyl (Dulcolax): an Evacuant Suppository. A Controlled Therapeutic Trial in Chronically Ill and Geriatric Patients," *Canadian Medical Association Journal*, 83:384-387, 1960.

(4) Berk, M.S., "Comparative Study of Bowel Control in Nursing Home Patients," *Medical Times*, 97:106-112, 1969.

(5) Jackson, B., "Clinical Trial of a New Drug in Obstinate Constipation," *Canadian Nurse*, 54:1107-1109, 1958.

(6) Rider, J.A., "Treatment of Acute and Chronic Constipation With Bisoxatin Acetate and Bisacodyl: Double-Blind Crossover Study," *Current Therapeutic Research*, 13:386-392, 1971

(7) Broatch, D.L., A. Wilson, and J. Thompson, "The Treatment of Constipation in the Elderly," *Nursing Times*, November 29, 1968.

(8) Christopher, L.J., "A Controlled Trial of Laxatives in Geriatric Patients," *Practitioner*, 202:821-825, 1969.

(9) Happert, J.L., "Clinical Trials of a New Contact Laxative," *Gaz. Hop., 135:1145-1148, 1963.*

(10) Neff, F.M., "Some Problems in the Management of Constipation," *California Clinician*, November, 1961.

(11) Niswander, L.C., "Bowels Can Be Retrained and Controlled," *Hospital Management*, 93: 6, 8, and 10, 1962.

(12) Wolcott, L.E., "Laxation In Patients With Chronic Disease Utilizing Bisacodyl," *Archives of Physical Medicine and Rehabilitation*, 44:375-377, 1963

(13) Letter from William E. Gilbertson, FDA, to Pam C. Mead, Boehringer Ingelheim, Ltd., coded ANS LET 010, Docket No. 78N-036L, Dockets Management Branch.

77. One comment recommended that the daily dosage of 750 to 900 mg for dehydrocholic acid recommended by the Panel in § 334.18(f) be changed to 750 to 1,000 mg. The comment pointed out that the "National Formulary" (Ref. 1) provides a dosage of 500 mg three times daily, which gives a maximum daily dose of 1,500 mg. The comment stated that, in view of the low toxicity of dehydrocholic acid, an increase in the maximum daily dose from 900 mg to 1,000 mg should be acceptable. Lastly, the comment pointed out that the "Physicians' Desk Reference" (Ref. 2) and "Facts and Comparisons" (Ref. 3) list only a 250-mg tablet strength for dehydrocholic acid and, as such, the recommended 900 mg maximum daily dosage would be difficult to obtain.

The agency has reviewed the data submitted to the Panel for dehydrocholic acid (Refs. 4 and 5) and notes that they provide for a single ingredient product to be marketed as a 250-mg tablet with a dosage in multiples of 250 mg, i.e., one or two tablets three times a day. This dosage provides a maximum daily dose of 1,500 mg. Also, in the minutes of its November 16, 1973 meeting, the Panel found dehydrocholic acid to be safe and effective at a maximum daily dose of 1,500 mg. Therefore, the dosage for dehydrocholic acid provided in the Panel's report and recommended monograph is in error and the tentative final monograph is revised to provide for a daily dose of 750 to 1,500 mg.

References

(1) "The National Formulary," 14th Ed., American Pharmaceutical Association, Washington, pp. 171-172, 1975.

(2) "The Physicians' Desk Reference," 29th Ed., Medical Economics Co., Oradell, NJ, 1975.

(3) "Facts and Comparisons," Facts and Comparisons, Inc., St. Louis, 1975.

(4) OTC Volume 090079.

(5) OTC Volume 090097.

78. One comment pointed out that a harmless pink or orange discoloration may appear in alkaline urine when laxatives containing phenolphthalein are used and urged that an explanation statement to that effect be included in the labeling. Another comment suggested that such a statement might mislead the consumer into thinking that discolored urine was always to be disregarded, whereas discoloration may indicate the presence of glomerulonephritis, tumors, and other serious conditions.

The Panel was aware that up to 15 percent of a therapeutic dose of phenolphthalein may be absorbed and excreted by the kidney, giving a pink color to alkaline urine (40 FR 12910). However, the Panel apparently did not consider this discoloration to be of signification concern to require a warning. The agency concurs with the Panel's decision and agrees with the second comment that requiring a warning about pink or orange discoloration may mislead consumers. A warning would be more confusing than helpful and is not necessary for the short-term safe use of OTC laxatives containing phenolphthalein.

H. Comments on Stool Softener Laxatives

79. Several comments objected to the classification of "stool softeners" as "laxatives." The comments contended that it was incorrect and misleading to apply the term "laxative" to these agents when used alone because they do not increase peristaltic activity or act directly on the bowel, but merely penetrate and soften the stool to ease

passage. One comment argued that the use of the term "laxative" in connection with single-ingredient stool softeners would be misleading because it would imply to consumers that the product would promote a relatively quick laxative effect. One comment urged that single-ingredient stool softeners as labeled as a "a stool softener and aid in the relief of constipation." Another comment suggested that such products be labeled as "non-laxative constipation remedies" and/or "for the prevention and treatment of constipation."

The agency disagrees with these comments for several reasons. Stool softeners are chemically distinct from other classes of laxatives in that they are surface-active agents that lower surface tension. Mixed in the stool, they allow sufficient water and fat penetration to have a softening effect on the stool, thus permitting easier bowel movement (Ref. 1). Although stool softeners affect the stool rather than the bowel, their action is consistent with the broad definition of a laxative as being "any agent used for the relief of constipation." This definition of laxatives does not distinguish whether the agency acts on the bowel to increase peristaltic activity or on the stool itself, so long as it acts to relieve constipation. The mode of action of stool softeners is not sufficiently different from that of other laxative agents to warrant their differentiation from other types of laxatives, but these products should be labeled as "stool softener laxatives" in order to provide the best information to the consumer.

The agency is proposing in the tentative final monograph that a time frame for expected relief of constipation be included in the labeling of stool softener laxatives (see comment 23 above.) Therefore, it appears unlikely that the consumer will be misled into expecting "quick" laxation with a stool softener laxative.

Reference

(1) Fingl, E., "Laxatives and Cathartics" in "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A Gilman, Macmillian Publishing Co., Inc., New York, pp. 977–986, 1975.

80. Two comments argued that the warning in recommended § 334.50(c)(3) and § 334.62(a) limiting use to 1 week should not apply to single-ingredient stool softener laxatives. The comments argued that this limitation was inappropriate because stool softeners act on the stool and not on the bowel, thus their action does not affect bowel function. One of the comments suggested that the labeling restriction be revised to read, "Caution: Not for prolonged use unless directed by a physician." Several other comments contended that the general warning in recommended § 334.50(c)(3), "this product should not be used for a period of longer than 1 week except under the advice and supervision of a physician", and the specific ingredient warning for stool softeners in recommended § 334.62(a), "This product should be used only occasionally, but in any event no longer than daily for 1 week," are duplicative and that the specific warning in § 334.62(a) should be eliminated.

Although stool softeners do not act directly on the bowel, they do soften the stool and thereby aid in evacuating the stool, thus relieving constipation. As discussed by the Panel in its report (40 FR 12906), when it is necessary to use any laxative, including stool softeners, to facilitate the evacuation of the bowel for more than 1 week, the cause of the constipation should be investigated by a doctor because a sudden change in bowel habits may be an indication of serious disease.

However, the agency agrees that the general warning in recommended § 334.50(c)(3) is duplicative of recommended § 334.62(a) and therefore, the Panel's recommended warning in § 334.62(a) is not included in the tentative final monograph.

81. One comment requested that d-calcium pantothenate be classified as a Category I stool softener ingredient, contending that the Panel's classification of d-calcium pantothenate as a Category III stimulant laxative was incorrect. According to the comment, d-calcium pantothenate has been and is a stool softener, not a stimulant, laxative. The comment submitted one clinical study (Ref. 1), which, it claimed, demonstrates that this ingredient is a Category I stool softener laxative. The comment also stated that, to its knowledge, no untoward side effects have been experienced with a combination product containing d-calcium pantothenate.

The agency notes that "calcium pantothenate" is the USP and USAN name for "calcium D-pantothenate." The only study submitted in support of the classification of calcium pantothenate as a Category I stool softener was conducted using calcium pantothenate in combination with the Category I stimulant laxative danthron. The study is inadequate because no comparison was made between the combination and the two ingredients contained in the combination when used alone. No objective measurements or analysis were made, e.g. stool weight/volume, transit time, etc. The only data analysis that is provided with the study is an analysis of "panelist's preference", which is not a valid measurement of laxative effectiveness. Further, no data are provided that support the comment's claim that calcium pantothenate is a stool softener laxative as opposed to the Panel's classification as a stimulant laxative. Therefore, it will be necessary to provide additional effectiveness data before the agency may reclassify calcium pantothenate as a Category I stool softener laxative. Although the Panel also recommended at 40 FR 12918 that safety studies should be provided, the agency believes that further safety studies are unnecessary. Pantothenic acid, the active constituent of calcium pantothenate, is a common water-soluble vitamin that is present in all human tissues. It has no outstanding pharmacodynamic action and is essentially nontoxic.

The agency's comments and evaluation on the data are on file in the Dockets Management Branch (Ref. 2).

References

(1) Comment No. 23, Docket No. 78N–036L, Dockets Management Branch.

(2) Letter from William E. Gilbertson, FDA, to Raymond Spector, C.F. Kirk Laboratories, Inc., coded ANS LET 006, Docket No. 78N–036L, Dockets Management Branch.

I. Comment on Miscellaneous Laxatives

82. One comment requested that recommended § 334.22 be revised to provide for a carbon dioxide-releasing suppository consisting of 0.6 g sodium bicarbonate and 0.9 g potassium bitartrate, releasing approximately 90 mL carbon dioxide per suppository. The comment submitted two references in support of its request (Refs. 1 and 2). The comment stated that the directions for use are the same as for the product identified in recommended § 334.22(a).

The two studies submitted by the comment support the inclusion of the suppository in the monograph. The study be Bolton and Benson (Ref. 1) was an open trial in which 321 patients were given one rectal suppository on the morning of the second post-partum day to re-establish bowel function. The patients were questioned and 70.5 percent reported that they experienced effective bowel movements. In 61 percent the urge to evacuate occurred within 30 minutes after administering the suppository. Banner (Ref. 2) reported that use of a single suppository was successful in approximately 60 to 65 percent of patients. Use of a second suppository 30 minutes after the first one in some patients increased efficiency by 5 percent. He also concluded that the suppository is a

satisfactory substitute for enemas during the postpartum state. The Panel (FR 12913 recognized the safety and effectiveness of carbon dioxide-releasing suppositories by including another carbon dioxide-releasing suppository in the monograph (containing sodium biphosphate, sodium acid pyrophosphate, and sodium bicarbonate). Although the tartrate/bicarbonate suppository releases less carbon dioxide than the one in the recommended monograph (90 mL as compared with 230 mL), experience with this suppository demonstrates its safety and effectiveness. Therefore, the tartrate suppository is included in this tentative final monograph.

References

(1) Bolton, R. N., and R. C. Benson, "A Unique Post Partum Rectal Suppository," *Obstetrics and Gynecology*, 13:501–503, 1959.

(2) Banner, E. A., "Rectal Suppositories as Substitutes for Enemas in the Post Partum Period," *Staff Meetings of the Mayo Clinic*, 28:567–568, 1953.

J. Comments on Laxative Combinations

83. Several comments objected to the Panel's recommendation to limit the number of laxative active ingredients allowed in a combination product (40 FR [illegible]22). The comments criticized the [illegible]el for seeking an absolute prohibition against combinations of three or more active ingredients based solely on what the comments characterized as subjective and arbitrary opinion. The comments stated that the Panel's recommendation was not founded upon scientific documentation and conflicts with both the Panel's and FDA's expressed willingness to permit manufacturers to show the rationality of a combination laxative product by demonstrating that each ingredient makes a therapeutic contribution to the overall effectiveness of the product. One comment stated that a prohibition against combining more than two ingredients required data establishing a possible risk of toxicity, synergistic effect, allergies, idiosyncratic reactions, or drug interactions.

The agency agrees with the comments that a fixed limit need not be set on the number of active ingredients a laxative drug product may contain. However, the agency believes the consumer is little served by a product containing multiple ingredients if laxation can be achieved safely and effectively by a smaller number of ingredients. Both the General Guidelines for OTC Drug Combination [illegible]cts (Ref. 1) and the regulations at 21 [illegible]R 330.10(a)(4)(iv) provide that an OTC drug product may combine two or more safe and effective active ingredients provided the product meets the combination policy in all respects.

If a manufacturer can show that a laxative combination meets the general guidelines for OTC combination drug products, the agency will have no objection to the product containing two or more Category I laxative ingredients. However, the comments did not submit any data to support specific combinations containing more than two laxative active ingredients. New data in support of such combinations may be submitted for up to 12 months following the publication of this document. Also, the agency has evaluated the Panel's combination formula in recommended § 334.31(b) in relation to marketed combination laxative products, the regulations (§ 330.10(a)(4)(iv)), and the combination guidelines (Ref. 1) and concludes that the formula allows those combinations of laxative ingredients identified in § 334.32 to meet these criteria for safe and effective OTC use. Combinations containing more than two laxative ingredients would also have to comply with the requirements of this formula. Any manufacturer wishing to market a product that is not within the specifications of the formula may submit data to support such a request.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D–0322, Dockets Management Branch.

84. Several comments stated that the Panel failed to provide a mechanism for manufacturers to have Category II and Category III combination drug products reclassified to Category I status except through a citizen petition or a new drug application. Further, the comments argued that the Panel, by limiting the Category I combinations to those listed in recommended § 344.32, was denying manufacturers the opportunity to develop and submit data in the future for establishing additional combinations as Category I. The comments urged the agency to reject the Panel's recommendation.

The agency agrees that the Panel was in error in implying that the only mechanism for reclassifying Category II or Category III combinations was through a citizen petition or the new drug procedures. There are several mechanisms by which data can be submitted to reclassify Category II and III combinations to Category I. The OTC drug review regulations provide for new data to be submitted during the 90-day comment period following publication of the Panel's report. New data and information to support conditions excluded from the monograph may be filed for 12 months following the publication of this tentative final monograph in accordance with the revised Category III procedures published in the Federal Register on September 29, 1981 (46 FR 47730). In all cases, data demonstrating a combination to be generally recognized as safe and effective must be submitted before a new combination can be included in the monograph.

85. One comment expressed the opinion that one of the underlying policy reasons for the OTC drug review is to facilitate the reformulation of combination products. Specifically, the comment stated that where a combination contains a Category III ingredient, the manufacturer should be permitted to replace the Category III ingredient with a similar Category I ingredient, so long as the product is otherwise appropriately formulated and labeled.

The agency agrees with the concept expressed by the comment but points out that the combination product resulting from such a reformulation must be among the Category I combinations listed in this tentative final monograph.

86. One comment was concerned that the Panel made no judgments with respect to the rationality of the combinations it recommended for Category III status. The comment noted that, in approving Category I combinations, the Panel applied its criteria for determining Category I combinations (40 FR 12921), and in so doing actually expressed a judgment that only these combinations are rational concurrent therapy for a significant proportion of the target population. The comment concluded that it should not be "presumed" that all other combinations are irrational in the absence of an express judgment by the Panel.

The agency agrees. The Panel did not express an opinion regarding the rationality of every specific combination. Therefore, there may be rational combinations that are not specifically listed in Category I.

87. Two comments objected to the Panel recommending the allowable OTC laxative [illegible]d in recommended § 334.32. One comment argued that specifying the ingredients allowed in a combination as is done in recommended § 334.32 (i.e., from individual products) is inappropriate. The comments suggested that any combination of Category I ingredients from a particular drug class such as laxatives, be permitted as long as the combination is in accord with the

general standards stated in § 330.10(a)(4) and the combination policy stated in § 330.10(a)(4)(iv).

These comments were submitted before the agency's guidelines for OTC combination products became available in 1978 (Ref. 1). Paragraph 6 of these guidelines states that final OTC drug monographs will list the specific ingredient combinations permitted for marketing under the monograph. Thus, the Panel's recommendations in § 334.32 are consistent with the current guidelines.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D-0322, Dockets Management Branch.

88. Several comments recommended revising recommended § 334.32 to list permitted combinations by pharmacological class rather than by specific ingredient. The comments pointed out that the specified combinations of ingredients actually represent 10 types of combinations by pharmacological class, i.e., bulk/bulk, bulk/lubricant, bulk/stimulant, bulk/stool softener, lubricant/stimulant, lubricant/saline, saline/stimulant, stimulant/stimulant, stimulant/stool softener, and stool softener/hyperosmotic. The comments argued that because the Panel found the specific ingredients in each of these pharmacological classes to be safe and effective, every ingredient in each class should be safe and effective in a combination and should be interchangeable.

Criteria for establishing combinations as Category I are provided in the OTC Combination Guidelines (Ref. 1). Paragraph 6 of these guidelines states, "In those cases where the data are sufficient to support a finding by the agency that several ingredients in a therapeutic category can be considered interchangeable for purposes of formulating combinations, the monograph will so state and list those ingredients. This is the preferred approach and will be done whenever supported by data and the opinion of experts." Therefore, the agency agrees with the concept of listing combination drug products by pharmacological class, but does agree that sufficient data have been provided to allow all of the laxatives in each class to be interchanged randomly for the purpose of forming combinations. Further, as pointed out in comment 22 above, the precise mechanisms of action of laxative ingredients are not well known and insufficient data are available on their combined effects. Therefore, the combination section of the tentative final monograph is revised to group the Panel's recommended combinations by pharmacological class. However, it has not been revised to allow all of the ingredients in a class to be used interchangeably. Combinations for which adequate data exist have been included in the monograph. However, data are necessary to establish the safety and effectiveness of other specific combinations or to demonstrate that the specific ingredients in a pharmacological class are chemically and pharmacological interchangeable.

Reference

(1) Food and Drug Administration "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D-0322, Dockets Management Branch.

89. Two comments requested that the monograph be expanded to include "bowel cleansing systems," i.e., products containing several different laxative ingredients for sequential administration at specified intervals, for use in evacuating the bowel prior to surgery, colon x-ray, or endoscopic examination. The comments contended that this special use of laxatives is not covered by the Panel's recommended monograph even though such products are being sold OTC. The comments submitted studies (Refs. 1 and 2) on the use of two different bowel cleansing systems: (1) Magnesium citrate oral solution, bisacodyl tablets, and bisacodyl suppositories and (2) magnesium citrate oral solution, phenolphthalein, and sodium bicarbonate-sodium bitartrate (carbon-dioxide releasing) suppositories.

The agency reviewed the data submitted by the comments and Tentatively concludes that the two bowel cleansing systems are generally recognized as safe and effective for use in evacuating the bowel prior to surgery, colon x-ray, or endoscopic examination. The agency agrees with the comments that these bowel cleansing systems should be included in the OTC monograph and is proposing a statement of identity and a definition for these products in this tentative final monograph. However, the agency does not believe that bowel cleansing systems should be used for general laxative purposes and, therefore, is proposing to limit their indication to the following: "For use as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for x-ray or endoscopic examination. In addition, the following warning is being proposed for these products in lieu of the general warnings in recommended § 334.50(c)(1) thru (4): "Do not use this product unless directed by a doctor." The agency also recognizes that in most of the submitted studies the bowel cleansing system was part of an overall regimen that included overhydration and certain dietary restrictions. Therefore, in addition to the appropriate directions for use for each laxative component of the bowel cleansing system, the agency is proposing to require manufacturers to supply information regarding fluid and dietary restrictions.

References

(1) Comment No. C00015, Docket No. 78N-0036L, Dockets Management Branch.

(2) Comment No. C00043, Docket No. 78N-0036L, Dockets Management Branch.

90. One comment argued that the Panel's restriction on the concurrent use of vitamins and minerals with a laxative should not apply to dietary bran products that are sold as cereals. The comment pointed out that FDA favors the fortification of cereals with vitamins and minerals (see the **Federal Register** of June 14, 1974; 39 FR 20989). The comment also disagreed with the Panel's position that a significant target population does not exist for concurrent use of laxatives with vitamins and minerals. The comment stated that people over 50 years of age often require vitamins and minerals concurrently with laxatives becuase if is well documented that the elderly are often on inadequate diets (Refs. 1 and 2). The Comment concluded that when the Panel stated that vitamins and minerals should not be added to laxative products, the Panel had drug type laxatives in mind and not cereals.

The agency agrees with the comment. As discussed in comment 38 above the agency does not intend to regulate in this monograph high fiber cereals that are offered only as foods.

References

(1) Rao, D. B., "Problems of Nutrition in the Aged," *Journal of the American Geriatrics Society*, 8:363-367, 1973.

(2) Smith, A. N. E., "Nutrition Survey and Problems of Detection of Malnutrition in the Elderly," *Nutrition*, 4:218-223, 1970.

91. One comment concurred with the Panel's finding at 40 FR 12916 that there is no evidence that the addition of vitamins and minerals to a laxative preparation contributes to a laxative effect and that constipation and vitamin needs ordinarily bear no relationship to each other. The comment noted, however, that the Panel apparently did not decide that minerals were unrelated to constipation. According to the comment, this fact constituted a silen'

recognition by the Panel of the constipating effect of iron. The comment pointed out that its combination vitamin and mineral products also contain a stool softener laxative. the comments stated that these products have never claimed a laxative effect and that the stool softener ingredient is included solely to overcome the constipating effect of iron.

There are two aspects to this comment: (1) The addition of vitamins/minerals to a laxative drug product intended primarily for laxative use and (2) the addition of an ingredient to a vitamin/mineral product for the purpose of alleviating the constipating effects of iron.

In the first case, the Panel concluded "that the addition of various vitamins and minerals, including trace elements, to laxative products is irrational concurrent thereapy and places such combinations in Category II." The agency concurs with this conclusion because a target population which could benefit from such combinations has not been adequately demonstrated. Vitamin/mineral deficiency and constipation do not routinely occur concurrently, thus the need for such a combination does not exist. In addition, OTC laxative drug products are intended only for occasional short-term use, whereas vitamins and minerals are normally taken daily for long-term dietary supplementation.

In the second case (the addition of an ingredient to a vitamin-mineral product to overcome the constipating effects of iron), the agency recognizes that iron may be constipating in some people. However, vitamin/mineral products that are intended for dietary supplementation are considered to be foods and ingredients added to them are also regulated under the food provisions of the Federal Food, Drug and Cosmetic Act.

92. One comment requested that 3 g psyllium seed (blond) and 30 mg casanthranol in combination be recognized as Category I. The comment argued that both ingredients were Category I laxatives and that a similar combination containing psyllium and senna concentrate was recognized as Category I. According to the comment, the Panel's only reason for failing to place the combination of psyllium seed (blond) and casanthranol in Category I was that it was unaware that a product, with only a slight difference in composition from the proposed Category I combination, had been marketed for 25 years with no known safety of effectiveness problems.

The Panel recognized the rationality of combining bulk laxatives with stimulant laxatives and included a combination containing psyllium and senna in the recommended monograph. Because senna and casanthranol are chemically and pharmacologically related anthraquinone laxatives, the agency believes it is rational to include in the monograph the combination mentioned in the comment. Accordingly, this combination is proposed as Category I in this tentative final monograph.

93. A comment requested that the combination of karaya gum and cascara sagrada be added to the list of Category I laxative combinations recommended § 334.32. The comment submitted data to establish that this combination of two Category I ingredients meets all criteria established by the Panel, as well as all criteria set forth in § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)) for Category I combination drug products.

The agency has reviewed the data submitted by the comment and has determined that the data provide support for the safety of the two ingredients when combined. The data consisted chiefly of acute oral toxicity and laxative effectiveness studies in Sprague-Dawley rats. Effectiveness studies in humans are needed. These studies should show that the conbination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Therefore, the agency considers this combination a Category III combination and has not included it in the tentiative final monograph.

94. A comment, which was accompanied by a single supporting study (Ref. 1), requested that the combination of danthron (75 mg) and sodium lauryl sulfate (25 mg) be placed in Category I as a combination laxative product.

The study cited by the comment was designed to determine the adjuvant effect of sodium lauryl sulfate, at levels of 100 to 200 mg, in buffering or lowering the threshold of abdominal discomfort from high doses (300 to 600 mg) of danthron. No data were presented on the combination at the dosage levels proposed by the comment nor were data presented demonstrating any effect of sodium lauryl sulfate other than as a pharmaceutical adjuvant to lower the side effects of danthron. Therefore, the combination is classified as Category III and is not included in the tentative final monograph.

Reference

(1) Marks, M. M., "A Clinical Evaluation of a New Cathartic Compound," *Diseases of the Colon and Rectum*, 4:131–133, 1961.

95. A comment pointed out that data for the combination of magnesium hydroxide and simethicone labeled for the indication "lower abdominal distress as a concomitant of constipation" were submitted to the OTC Miscellaneous Internal Drug Products Panel, but not to the Laxative Panel. The comment noted that the Laxative Panel concluded at 40 FR 12921 that "products combining laxative ingredient(s) with other ingredients having nonlaxative pharmacologic effects are considered irrational unless it can be shown that there is a significant target population requiring concurrent treatment of symptoms that require laxative(s) and nonlaxative(s) in combination." Because data on the combination of magnesium hydroxide and simethicone were neither submitted to nor considered by the Laxative Panel, the comment requested that the agency not take any classification action regarding this combination until the OTC Miscellaneous Internal Drug Products Panel had completed its review of the combination.

The agency notes the Miscellaneous Internal Panel in its report on OTC Digestive Aid Drug Products published in the **Federal Register** of January 5, 1982 (47 FR 454), classified magnesium hydroxide and simethicone, both alone and in combination, in Category III for the treatment of the symptoms of immediate postprandial upper abdominal distress and the symptoms of intestinal distress (lower abdominal distress).

In addition, that Panel further concluded that the intestinal distress syndrome (lower abdominal distress) is self-limited, not attributable to any known organic disease, and is not accompanied by constipation or diarrhea.

The comment included no data to demonstrate the effectiveness of the combination of magnesium hydroxide and simethicone or to show that there is a significant target population requiring concurrent treatment of lower abdominal distress and constipation. Therefore, the agency is unaware of any data to establish that lower abdominal distress and constipation occur concomitantly or that the combination of magnesium hydroxide and simethicone is safe and effective for the idication proposed by the comment. Accordingly, the combination is Category II in this laxative tentative final monograph.

96. Two comments urged that recommended § 334.32(a) (10), (11), (12), and (14) be revised to permit the use of mineral oil emulsion as an alternative

ingredient for combinations of plain mineral oil with casanthranol, cascara sagrada, cascara sagrada fluid extract, and phenolphthalein, respectively. The comments pointed out that a number of the pertinent combination laxative drug products considered by the Panel in recommending these permitted combinations do in fact contain mineral oil in the form of mineral oil emulsion. The comments argued that it is inconsistent to classify plain mineral oil as an allowable ingredient in these combinations and to exclude mineral oil emulsion as an alternative ingredient in the same combination.

As discussed in comment 47 above, the agency has deleted reference to mineral oil emulsion from the monograph. Although manufacturers may choose to formulate the allowable mineral oil combination in an emulsion formulation, the monograph will list only mineral oil as the active ingredient in the allowable combinations.

97. One comment requested that the combination of calcium pantothenate and danthron be classified as Category I. The comment submitted data (Ref. 1) which, it claimed, demonstrate that the combination of calcium pantothenate and danthron is as effective as the Category I combination of docusate sodium and danthron.

The agency tentatively concludes that the data submitted are insufficient to support reclassifying the combination of danthron and calcium pantothenate into Category I. The same study was submitted to support calcium pantothenate as a single ingredient. (See comment 81 above.) Because no comparisons were made of the combination and the ingredient alone, the contribution of the ingredients to the combination has not been shown. In addition, the study had other problems that have already been discussed in comment 81 above. Therefore, the combination of danthron and calcium pantothenate remains in Catgeory III in this tentative final monograph.

Reference

(1) Comment No. 00023, Docket No. 78N-036L, Dockets Management Branch.

K. Comments on Data Pertinent for Laxative Ingredient Evaluation

98. Several comments addressed the testing guidelines recommended to move a laxative ingredient from Category III to Category I. Some comments were opposed to the guidelines, indicating that they were unclear, unnecessary, inconsistent, and possibly confusing. Other comments indicated that the testing guidelines provided inadequate time to complete the required testing. One comment stated that manufacturers should be allowed to use other well-controlled and well-designed studies to obtain necessary data and should not be restricted to using only the types of tests mentioned in the guidelines.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part III. paragraph A.2. below—Testing of Category II and Category III conditions.)

II. Agency Initiated Changes

1. The Panel recommended infant dosages for a number of laxative ingredients and comments were received recommending infant dosages for still more laxative ingredients. (See part I. comments 45 and 54 above.)

The agency is, however, concerned that constipation in infants may be a sign of a more serious condition that should be properly diagnosed by a doctor. Such conditions can include gastroenteritis, Hirschsprung's disease, congenital anal fissure, and anatomical abnormalities (Refs. 1 and 2).

In a study of constipation in 138 children, 14.5 percent (20) were found to have a disease that accounted for this symptom. Eight of these children, age 1 to 3½ years, were found to have anal fissures so severe as to require fairly vigorous medical or surgical treatment. The remaining 12 children were found to have a variety of problems including anatomical abnormalities of the anus and of the internal nervous system. The fact that 14.5 percent of the total group had diseases that accounted for the sympton of constipation empasizes the need for consulting a doctor in cases of infant constipation (Ref. 3).

Constipation is rare in breast-fed infants who receive an adequate amount of milk and in artificially fed infants who receive an adequate diet. The criterion for determining infant constipation is the nature for consistency of the stool and not its frequency. Most infants will have one or more stools daily, but some infants will pass a stool of normal consistency only at intervals of 36 to 48 hours (Ref. 4).

In view of the relative rarity of simple constipation in infancy and the high risk that it may be a sign of serious disease, anatomical abnormality, or an inadequate diet that should be properly diagnosed by a doctor, the agency is proposing that dosages for children under 2 years of age not appear in the OTC labeling. Dosages for children under 2 years of age are being included in the tentative final monograph only under professional labeling.

References

(1) Levine, M.D., "Children with Encopresis: A Descriptive Analysis," *Pediatrics*, 56:412–418, 1975.

(2) Bentley, J.F.R., "Progress Report: Constipation in Infants and Children," *GUT*, 12:85–90, 1971.

(3) Mercer, R.D., "Constipation," *The Pediatric Clinic of North America*, 14:175–185, 1967.

(4) "Textbook of Pediatrics," 11th Ed., edited by Wald E. Nelson, W.B. Saunders Co., Philadelphia, p. 208, 1979.

2. The agency concludes that the warning in recommended § 334.64(c), "Rectal bleeding or failure to evacuate may indicate a serious condition and a physician should be consulted", should apply to all laxative products and not just to one specific class of laxatives. Therefore, this warning is revised in this tentative final monograph to read: "Rectal bleeding or failure to have a bowel movement after use may indicate a serious condition. Discontinue use and consult your doctor." The agency is proposing that all laxative drug products be labeled with this warning as specified in this tentative final monograph at § 334.50(b)(4).

3. The Panel's recommended general warnings for sodium containing laxatives are not consistent with the sodium warnings required for antacid drug products (21 CFR 331.30(b)(5)). To resolve this inconsistency the agency proposes in this tentative final monograph that the sodium-restricted diet warning apply to all laxative products containing more than 5 mEq (115 mg) of sodium in the maximum recommended daily dose and that the kidney disease warning recommended by the panel be deleted. The agency proposes, however, to retain the Panel's recommended warning requiring a statement of sodium content per dosage unit for all laxative products containing more than 1 mEq (23 mg) of sodium per maximum daily dose because it is more informative than the one in the antacid monograph (21 CFR 331.30(e)). The agency invites comment on this proposal.

4. The agency has reviewed the warnings for phosphate-containing

laxatives and notes that one warning cautions against oral use of phosphate-containing laxatives by children under 6 years of age. The dosage and directions for use of such products in this tentative final monograph are for children 5 years of age and over because these products traditionally have been used in this age group. In order to eliminate the inconsistency the age limit in the warning in this tentative final monograph is revised to 5 years of age.

5. The agency has reviewed the Panel's definitions in recommended § 334.3 and has eliminated several terms from this section as unnecessary and redundant because their meaning is clear within the context of the monograph. However, two new terms, "carbon dioxide-releasing laxative" and "bowel cleansing system," have been added to the definitions in § 334.3 of this tentative final monograph because their meanings are not adequately clarified within the context of their use in the monograph.

6. The agency recognizes that saline laxatives may be irritating and cause nausea if taken with insufficient amounts of liquid (Refs. 1 and 2). In addition, saline laxatives are recommended to be taken with a full glass of water to achieve their maximum effect (Ref. 3). Therefore, in this tentative final monograph the agency proposes the direction to "drink a full glass (8 oz of liquid with each dose" for both bulk-forming and saline laxatives.

References

(1) Grollman, A., "Pharmacology and Therapeutics," Lea and Febiger, Philadelphia, p. 625, 1965.

(2) Bowman, W.C., and M.J. Rand, "Textbook of Pharmacology," Blackwell Scientific Publications, Oxford, England, p. 25.34, 1980.

(3) "United States Pharmacopeia Dispensing Information—1981," 2d Ed., United States Pharmacopeial Convention, Inc., Rockville, MD, p. 924.

7. It is unlcear whether the glycerin enema dosage in recommended § 334.12(a) refers to the total volume of enema solution or to the amount of glycerin in the enema solution. Because the data on safety and effectiveness of glycerin enema reviewed by the Panel was for an 80-percent solution of glycerin (Ref. 1), this tentative final monograph is revised to reflect that the dosage statement for glycerin enema is for an 80-percent glycerin solution.

Reference

(1) OTC Volume 090025, Docket No. 78N-[illegible], Dockets Management Branch.

The agency has reviewed the Panel's recommended warnings for castor oil-containing products advising against regular use (recommended § 334.60(c)). The agency believes that the revised indications and warnings proposed in this tentative final monograph for all laxative drug products sufficiently guard against regular use. Therefore, the agency is not including the Panel's recommended warnings for castor oil in this tentative final monograph.

9. The agency has reviewed the various studies submitted to support the professional use of laxative ingredients for use in preparing the colon for x-ray and endoscopic examination and/or for preparing the patient for surgery. In most of the studies submitted the laxative ingredients were not used alone, but were part of an overall regimen which included overhydration, dietary restrictions and/or other laxative agents. Therefore, in this tentative final monograph the agency proposes to modify the professional labeling indications for laxative ingredients used for bowel cleansing purpose to include the additional phrase, "for use as part of a bowel cleansing regimen."

III. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's categorization of ingredients. For the convenience of the reader, the following table is included as a summary of the categorization of OTC laxative active ingredients.

Laxative active ingredients	Category
Bulk-forming laxatives:	
Agar	III.
Alpha cellulose	III.
Bran	I.
Calcium polycarbophil	I.
Carrageenan, degraded	II.
Carrageenan, native	III.
Guar gum	III.
Karaya	I.
Malt soup extract	I.
Methylcellulose	I.
Polycarbophil	I.
Psyllium ingredients	I.
Plantago ovata husks	
Plantago seeds	
Psyllium (hemicellulose)	
Psyllium, hydrophyllic mucilloid (psyllium hydrocolloid)	
Psyllium seed	
Psyllium seed (blond)	
Psyllium seed husks	
Sodium carboxymethylcellulose	I.
Hyperosmotic laxatives:	
Glycerin	I.
Sorbitol	I.
Lubricant laxative: Mineral oil	I.
Saline laxatives:	
Magnesium citrate oral solution, USP	I.
Magnesium hydroxide	I.
Magnesium sulfate	I.
Sodium biphosphate	I.
Sodium phosphate	I.
Tartaric acid and salts	III.
Stimulant laxatives:	
Aloe	I.
Aloin	III.
Bile salts (acid) and ox bile	III.
Bisacodyl	I
Calcium pantothenate	III.
Calomel	II.
Cascara sagrada ingredients	I
Casanthranol	
Cascara fluidextract, aromatic	
Cascara sagrada bark	
Cascara sagrada extract	
Cascara sagrada fluidextract	
Castor oil	I.
Colocynth resin	II.
Danthron	I.
Dehydrocholic acid	I.
Elaterin resin	II.
Frangula	III.
Gamboge resin	II
Ipomea resin	II
Jalap resin	II
Phenolphthalein (white or yellow)	I.
Podophylum resin (podophyllin)	II.
Prune concentrate dehydrate and prune powder	III
Rhubarb, Chinese	III.
Sennosides A and B	I.
Sodium oleate	III.
Stool Softener Laxatives:	
Docusate ingredients [1]	
Docusate calcium sulfosuccinate	
Docusate potassium sulfosuccinate	
Docusate sodium sulfosuccinate	
Poloxalkal (polykol)	III
Carbon Dioxide-Releasing Laxatives:	
Released carbon dioxide from combined sodium biphosphate, anhydrous, sodium acid pyrophosphate, and sodium bicarbonate.	I.
Released carbon dioxide from combined, sodium biphosphate and sodium bitartrate.	I

[1] To be discussed in a separate FEDERAL REGISTER publication.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for laxative drug products (40 FR 12922). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any laxative ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made in the Panel's conclusions and recommendations follows.

1. Because of the number of changes that have been made, as summarized below, many of the section and paragraph numbers have been redesignated in this tentative final monograph. In addition, Subpart D has been redesignated as Subpart C, and the labeling sections of the monograph placed under Subpart C.

2. The following changes have been made to conform to the format and content of other recent OTC drug tentative final monographs:

a. A "statement of identity" section has been added for each laxative drug category.

b. The dosage information for each active ingredient has been moved to the directions section for the respective laxative drug category.

c. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

d. The signal word "warning" is being used in labeling instead of the signal word "caution." (See comment 27 above.)

3. Some of the Panel's recommended dosages did not specify the dosage interval but merely stated a daily dose. The tentative final monograph clarifies that the recommended dose is to be taken as a single daily dose. (See comment 12 above.)

4. The indication statement for laxative drug products has been revised to "For the relief of occasional constipation" [which may be followed by "(irregularity)."] (See comment 14 and 15 above.)

5. The professional labeling section has been revised to clarify that the required OTC labeling for a laxative drug product must be included in the labeling provided to health professionals. (See comment 21 above.)

6. The statement of identity for hyperosmotic laxatives is simply "laxative." (See comment 22 above.)

7. The tentative final monograph clarifies that the definitions of laxative drug categories need not appear in the labeling. However, the timeframes within which the different types of laxatives are expected to produce bowel movement are required in the labeling. (See comment 23 above.)

8. The definition of "short-term use" is not included in the tentative final monograph. (See comment 26 above.)

9. The phrase "this product" has been replaced with the phrase "laxative products" in those warning statements where the warning is applicable to all laxative products. (See comment 28 above.)

10. The drug interaction warning for cellulose derivatives is not included in the tentative final monograph. (See comment 35 above.)

11. The phrase "adequate liquid intake" in the directions of bulk-forming laxatives has been replaced with the phrase "Drink a full glass (8 oz) of liquid with each dose." The warnings recommended for bulk-forming laxatives that advised consumers to drink a full glass of liquid with each dose have been deleted because they are repetitious of the statements in the directions. In addition, the definition of "adequate liquid intake" is not included in the tentative final monograph. (See comment 36 above.)

12. The doseage of glycerin suppositories has been clarified to reflect the amount of glycerin per suppository. (See comment 45 above.)

13. The rectal use warning for glycerin products has been revised to read "For rectal use only." (See comment 46 above.)

14. Reference to mineral oil emulsion is not included in the tentative final monograph. The tentative final monograph includes warnings and directions for use for mineral oil only. (See comment 47 above.)

15. The warning for mineral oil products for persons who should not be administered mineral oil has been revised and does not contain a reference to "aged patients." (See comment 48 above.)

16. That portion of the warning for mineral oil products that warns not to administer mineral oil to persons having recent episodes of vomiting, regurgitation, or abdominal pain is not included in the tentative final monograph. (See comment 49 above.)

17. The drug interaction precaution for stool softener laxatives has been amended to include the phrase "unless directed by a doctor." (See comment 50 above.)

18. Specific sequestering agents for magnesium citrate in oral solution are not included in the tentative final monograph. (See comment 52 above.)

19. The dosage for magnesium citrate has been expanded to be compatible with USP requirements. (See comment 55 above.)

20. The professional labeling section of the tentative final monograph includes a professional indication for magnesium citrate and phosphate salts. (See comments 53 and 58 above.)

21. An infant dosage for magnesium hydroxide is included in the professional labeling section of the tentative final monograph. (See comment 54 above.)

22. The directions for the magnesium-containing saline laxatives have been amended to provide for a single daily dose. (See comment 56 above.)

23. The storage condition information for magnesium citrate oral solution has been revised to conform to the USP specifications. (See comment 57 above.)

24. The dosages for the phosphate salts have been revised. (See comment 58 above.)

25. The directions for saline laxatives in this tentative final monograph include the phrase "Drink a full glass (8 oz) of liquid with each dose." (See part II. paragraph 7 above.)

26. The general warnings for stimulant laxative drug products are not included in the tentative final monograph. (See comments 62 through 65 above.)

27. The dosages for the senna preparations have been revised to provide dosages for sennosides A and B only. (See comment 70 above.)

28. A suppository dose for sennosides A and B is included in the tentative final monograph. (See comment 70 above.)

29. The Panel's recommended monograph has been amended to include a bowel cleansing indication for a high dose of sennosides A and B. (See comment 70 above.)

30. The bisacodyl dosage have been revised to delete reference that the drug should be taken only at bedtime. (See comment 73 above.)

31. The warnings for bisacodyl products have been separated into two sections—one for enteric-coated tables, the other for the suppository. (See comment 74 above.)

32. The warning advising not to give bisacodyl enteric-coated tablets to children under 3 years of age has been revised to warn against the use of bisacodyl entreric-coated tablets in

children under 6 years of age. (See comment 74 above.)

33. The storage condition statement [illegible]odyl products has been revised to delete reference to the word "cool." (See comment 75 above.)

34. The dosage for dehydrocholic acid has been revised to provide for a dose of 250 to 500 mg three times a day. (See comment 77 above.)

35. The specific 1-week use limitation for stool softener laxatives is not included in the tentative final monograph. (See comment 80 above.)

36. A carbon dioxide-releasing suppository consisting of sodium bicarbonate and potassium bitartrate is included in the tentative final monograph. (See comment 82 above.)

37. The tentative final monograph provides for bowel cleansing systems. (See comment 89 above.)

38. A combination containing psyllium seed (blond) and casanthranol is included in the tentative final monograph. (See comment 92 above.)

39. Dosages for children under 2 years of age are included only in the professional labeling section of the tentative final monograph. (See part II. paragraph 1 above.)

40. The rectal bleeding warning recommended by the Panel for the [illegible]rbon dioxide-releasing suppositories [illegible]s been revised and is being recommended for all laxative drug products. (See part II. paragraph 2 above.)

41. The sodium warnings for laxative drug products have been revised to conform to the sodium warnings required in the antacid monograph. (See part II. paragraph 3 above.)

42. The warning for orally-[illegible]dministrated phosphate-containing [illegible]axative drug products advising against [illegible]se in children has been revised to be [illegible]consistent with the directions for use. See part II. paragraph 4 above.)

43. The agency has amended the definitions section of the monograph to delete unnecessary ones and to add new ones where necessary. (See part II. paragraph 5 above.)

44. The dosage for glycerin enema has been revised to reflect that the solution is an 80-percent concentration of glycerin. (See part II. paragraph 7 above.)

45. The agency has deleted the specific warnings recommended by the Panel for castor oil from the tentative final monograph. (See part II. paragraph 8 above.)

46. The agency has modified the [illegible]ssional labeling indications for [illegible]ive ingredients used in preparing the colon for x-ray and endoscopic examination and/or preparing the patient for surgery to reflect their actual use as part of bowel cleansing system. (See part II. paragraph 9 above.)

The agency proposes to revoke the existing warning and caution statements in § 369.20 for cathartics and laxatives and for mineral oil laxatives at the time this monograph becomes effective. The agency also proposes to revoke the existing regulations in § 201.302 for mineral oil at the time the final monograph becomes effective.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assesement of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC laxative drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary Regulatory Flexibility Analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC laxative drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC laxative drug products. Types of impact may include, but are not limited to, costs associated with products testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC laxative drug products should be accompanied by appropriate documentation. Because the agency has not previsously invited specific comment on the economic impact of the OTC drug review on laxative drug products, a period of 120 days from the date of publication of this proposed rulemaking in the Federal Register will be provided for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(a)(9) (propsoed in the Federal Register of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an enviornmental assessment nor an environmental impact statement is required.

Section 334.66(d)(3) of this proposed rule contains a collection of information requirement. As required by section 3504(h) of the Paperwork Reduction Act of 1980, FDA has submitted a copy of this proposed rule to the Office of Management and Budget (OMB) for its review of this collection of information requirement. Other organizations and individuals desiring to submit comments on this collection of information requirement should direct them to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Rm. 3208, New Executive Office Bldg., Washington, DC 20503, Attn: Bruce Artim.

List of Subjects in 21 CFR Part 334

OTC drugs: Laxative drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041-1042 as amended, 1050-1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11, it is a proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding new Part 334, to read as follows:

PART 334-LAXATIVE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Subpart B—Active Ingredients

Sec.

Subpart C—Labeling

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 334.1 Scope.

(a) An over-the-counter laxative drug product in a form suitable for oral or rectal administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this part and each general condition established in § 330.1.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 334.3 Definitions.

As used in this part:

(a) *Laxative.* Any agent used for the relief of constipation.

(b) *Laxation.* To cause a bowel movement.

(c) *Constipation.* Infrequent or difficult bowel movement.

(d) *Bulk-forming laxative.* An agent that increases bulk volume and water content of the stool thereby promoting bowel movement.

(e) *Carbon dioxide-releasing laxative.* A suppository dosage form containing several ingredients that release cabon dioxide, thereby inducing gentle pressure in the rectum which promotes bowel movement.

(f) *Hyperosmotic laxative.* An agent that attracts water into the stool thereby promoting bowel movement.

(g) *Lubricant laxative.* An agent that lubricates the contents of the intestinal tract thereby promoting bowel movement.

(h) *Saline laxative.* An agent that increases water in the intestine thereby promoting bowel movement.

(i) *Stimulant laxative.* An agent that promotes bowel movement by one or more direct actions on the intestine.

(j) *Stool softener laxative.* An agent that penetrates and softens the stool thereby promoting bowel movement.

(k) *Bowel cleansing system.* A laxative drug product containing several different laxative ingredients for sequential administration at specified time intervals, for use in cleansing the bowel prior to surgery, colon x-ray, or endoscopic exmination.

Subpart B—Active Ingredients

§ 334.10 Bulk-forming laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.52(d):

(a) Bran.

(b) Cellulose (semisynthetic) ingredients.

(1) Methylcellulose.

(2) Sodium carboxymethylcellulose.

(c) Karaya.

(d) Malt soup extract.

(e) Polycarbophil.

(f) Psylllium ingredients.

(1) Plantago ovata husks.

(2) Plantago seed.

(3) Psyllium (hemicellulose).

(4) Psyllium hydrophyllic mucilloid.

(5) Psyllium seed.

(6) Psyllium seed (blond).

(7) Psyllium seed husks.

§ 334.12 Hyperosmotic laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.54(d):

(a) Glycerin.

(b) Sorbitol.

§ 334.14 Lubricant laxative active ingredients.

The active ingredient of the product consists of mineral oil when used within the dosage limit established in § 334.56(d).

§ 334.16 Saline laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.58(d):

(a) Magnesium citrate.

(b) Magnesium hydroxide.

(c) Magnesium sulfate.

(d) Sodium phosphate/sodium biphosphate marketed as a solution.

(e) Sodium phosphate.

(f) Sodium biphosphate.

§ 334.18 Stimulant laxative active ingredients.

The active ingredient of the product consists of any of the following when used within the dosage limits established for each ingredient in § 334.60 (d):

(a) Aloe.

(b) Bisacodyl.

(c) Cascara sagrada ingredients.

(1) Casanthranol.

(2) Cascara fluidextract, aromatic.

(3) Cascara sagrada bark.

(4) Cascara sagrada extract.

(5) Cascara sagrada fluidextract.

(d) Castor oil.

(e) Danthron.

(f) Dehydrocholic acid.

(g) Phenolphthalein.

(h) Sennosides A and B from any of the following sources: senna leaf powder, senna fluidextract, senna fruit extract, senna syrup, senna pod concentrate, or sennosides A and B crystalline.

§334.20 Stool softener laxative active ingredients [Reserved].

§ 334.22 Carbon dioxide-releasing laxatives.

The active ingredient of the product consists of the following when used within the dosage limits established in § 334.64(d):

(a) Carbon dioxide released from combined sodium biphosphate anhydrous, sodium acid pyrophosphate, and sodium bicarbonate.

(b) Carbon dioxide released from combined sodium bicarbonate and potassium bitartrate.

§ 334.30 Permitted combinations of active laxative ingredients.

The active laxative ingredients of the product consists of a combination of ingredients listed below provided the combination meets the laxative criteria established in § 334.31.

(a) The following bulk laxative ingredients may be combined provided the combination is labeled according to § 334.52:

(1) Malt soup extract identified in § 334.10(d) and psyllium seed (blond) identified in § 334.10(f)(6).

(2) Malt soup extract identified in § 334.10(d) and psyllium seed husks identified in § 334.10(f)(7).

(3) Methylcellulose identified in § 334.10(b)(1) and plantago ovata husks identified in § 334.10(f)(1).

(b) The following bulk laxative ingredient may be combined with the following lubricant laxative ingredient provided the combination is labeled according to §§ 334.52.. and 334.56: Psyllium seed identified in § 334.10(f)(5) and mineral oil identified in § 334.14.

(c) The following bulk laxative ingredients may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.52 and 334.60:

(1) Psyllium (hemicellulose) identified in § 334.10(f)(3) and sennosides A and B identified in § 334.18(h).

(2) Psyllium seed (blond) identified in § 334.10(f)(6) and casanthranol identified in § 334.18(c)(1).

(d) [Reserved]

(e) the following lubricant laxative ingredient may be combined with the following stimulant laxative ingredients provided the combination is labeled according to §§ 334.56 and 334.60:

(1) Mineral oil identified in § 334.14 and casanthranol identified in § 334.18(c)(1).

(2) Mineral oil identified in § 334.14 and cascara sagradaextract identified in § 334.18(c)(4).

(3) Mineral oil identified in § 334.14 and cascara sagrada fluidextract identified in § 334.18(c)(5).

Mineral oil identified in § 334.14 a[illegible]henolphthalein identified in § 334.18(g).

(f) The following lubricant laxative ingredient may be combined with the following saline laxative ingredient provided the combination is labeled according to §§ 334.56 and 334.58: Mineral oil identified in § 334.14 and magnesium hydroxide identified in 334.16(b).

(g) The following saline laxative gredient may be combined with the llowing stimulant laxative ingredient ovided the combination is labeled cording to §§ 334.58 and 334.60: agnesium hydroxide identified in 334.18(c)(4).

(h) The following stimulant laxative ingredients may be combined provided they are labeled according toi § 334.60:

(1) Aloe identified in § 334.18(a) and casanthranol identified in § 334.18(c)(1).

(2) Cascara sagrada extract identified in § 334.18(c)(4) and phenolphthalein identified in § 334.18(g).

§ 334.31 Laxative.

(a) The sum of the precentages of the effective dosage range (EDR) as determined in paragraph (b) of this section for each active ingredient in the co[illegible]nations permitted in § 334.30 shall nc[illegible]ceed 100 percent.

(b) The method used for determining the EDR percentage value of each active ingredient is as follows:

$$\frac{\text{L max d} - \text{EDR (min)}}{\text{EDR (max)} - \text{EDR (min)}} \quad 100 = \%\ \text{EDR of each ingredient where:}$$

(1) L max d is the labeled maximum daily dosage of the ingredient which must be within the effective daily dosage range for the ingredient established in §§ 334.52, 334.54, 334.56, 334.58, 334.60, or 334.62.

(2) EDR (min) is the effective daily dosage range (minimum) and EDR (max) is the effective daily dosage range (maximum) for the active ingredient established in §§ 334.52, 334.54, 334.56, 334.58, 334.60, or 334.62.

§ 334.32 Bowel cleansing systems.

(a) A kit containing the following 3 laxative drug products for sequential administration as specified in § 334.66(d)(5): magnesium citrate identified in § 334.16(a) and bisacodyl identified in § 334.18(b) in both an oral dosage form and a suppository dosage form.

(b) A kit containing the following 3 laxative drug products for sequential administration as specified in § 334.66(d)(6): magnesium citrate identified in § 334.16(a), phenolphthalein identified in § 334.18(g) in an oral dosage form, and carbon dioxide-releasing suppositories identified in § 334.22(b).

Subpart C—Labeling

§ 334.50 Labeling of laxative drug products.

In addition to the labeling described in §§ 334.52, 334.54, 334.56, 334.58, 334.60, 334.62, and 334.64, the labeling of laxative drug products contains the following statements unless otherwise specified.

(a) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "For relief of occasional constipation" [which may be followed by "(irregularity)."]

(b) *Warnings.* The labeling of the product contains the following information under the heading "Warnings." If applicable, the warnings in this section may be combined with the warnings in §§ 334.58 and 334.60 to eliminate duplicative words or phrases so the resulting warning is clear and understandable.

(1) "Do not use laxative products when abdominal pain, nausea, or vomiting are present unless directed by a doctor."

(2) "If you have noticed a sudden change in bowel habits that persists over a period of 2 weeks, consult a doctor before using a laxative."

(3) "Laxative products should not be used for a period longer than 1 week unless directed by a doctor."

(4) "Rectal bleeding or failure to have a bowel movement after use of a laxative may indicate a serious condition. Discontinue use and consult your doctor."

(5) *For products containing more than 5 milliequivalents (115 milligrams) sodium in the maximum recommended daily dose.* "Do not use this product if you are on a low salt diet unless directed by a doctor."

(6) *For products containing more than 25 milliequivalents (975 milligrams) potassium in the maximum recommended daily dose.* "Do not use this product if you have kidney disease unless directed by a doctor."

(7) *For products containing more than 50 milliequivalents (600 milligrams) magnesium in the maximum recommended daily dose.* "Do not use this product if you have kidney disease unless directed by a doctor."

(8) A product containing more than 1 milliequivalent (23 milligrams) sodium per maximum daily dose shall be labeled as to the sodium content per dosage unit.

(c) *Directions.* The labeling of the product contains the appropriate directions identified in §§ 334.52, 334.54, 334.56, 334.58, 334.60, 334.62, 334.64, and 334.66 under the heading "Directions" followed by "or as directed by a doctor."

(d) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this subpart.

§ 334.52 Labeling of bulk-forming laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.10 includes the established name of the drug, if any, and identifies the product as a "bulk-forming laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the phrase: "This product generally

produces bowel movement in 12 to 72 hours."

(c) *Warnings.* The labeling of the product contains the applicable warnings identified in § 334.50(b) under the heading "Warnings."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing any ingredient identified in § 334.10.* "Drink a full glass (8 ounces) of liquid with each dose."

(2) *For products containing bran identified in § 334.10(a).* Adults and children 12 years of age and over: oral dosage is 6 to 14 grams. There is no maximum daily dose. Children under 12 years of age: consult a doctor.

(3) *For products containing methylcellulose and sodium carboxymethylcellulose identified in § 334.10(b) (1) and (2).* Adults and children 12 years of age and over: oral dosage is 4 to 6 grams in a single daily dose. Children 6 to under 12 years of age: oral dosage is 1 to 1.5 grams in a single daily dose. Children under 6 years of age: consult a doctor.

(4) *For products containing karaya identified in § 334.10(c).* Adults and children 12 years of age and over: oral dosage is 5 to 10 grams in a single daily dose. Children under 12 years of age: consult a doctor.

(5) *For products containing malt soup extract identified in § 334.10(d).* Adults and children 2 years of age and over: oral dosage is 12 to 64 grams in a single daily dose. Children under 2 years of age: consult a doctor.

(6) *For products containing polycarbophil identified in § 334.10(e).* Adults and children 12 years of age and over: oral dosage is 4 to 6 grams in a single daily dose. Children 6 to under 12 years of age: oral dosage is 1.5 to 3 grams in a single daily dose. Children 2 to under 6 years of age: oral dosage is 1 to 1.5 grams in a single daily dose. Children under 2 years of age: consult a doctor.

(7) *For products containing any psyllium ingredient identified in § 334.10(f).* Adults and children 12 years of age and over: oral dosage is 2.5 to 30 grams in a single daily dose. Children 6 to under 12 years of age: 1.25 to 15 grams in a single daily dose. Children under 6 years of age: consult a doctor.

§ 334.54 Labeling of hyperosmotic laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.12 includes the established name of the drug, if any, and identifies the product as a "laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the phrase: "This product generally produces bowel movement in ¼ to 1 hour."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statement under the heading "Warnings:"

(1) *For products containing glycerin identified in § 334.12(a).* "May cause rectal discomfort or a burning sensation."

(2) *For products containing glycerin or sorbitol identified in § 334.12 (a) and (b).* "For rectal use only."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing glycerin identified in § 334.12(a)*—(i) *Rectal suppository dosage.* Adults and children 6 years of age and over: rectal suppository dosage is 2 to 3 grams glycerin in a single daily dose. Children 2 to under 6 years of age: rectal suppository dosage is 1 to 1.7 grams glycerin in a single daily dose. Children under 2 years of age: consult a doctor.

(ii) *Rectal enema dosage.* Adults and children 6 years of age and over: rectal enema dosage is 5 to 15 milliliters of an 80 percent volume/volume solution in a single daily dose. Children 2 to under 6 years of age: rectal enema dosage is 2 to 5 milliliters as an 80 percent volume/volume solution in a single daily dose. Children under 2 years of age: consult a doctor.

(2) *For products containing sorbitol identified in § 334.12(b).* Adults and children 12 years of age and over: rectal enema dosage is 120 milliliters as a 25 to 30 percent weight/volume solution in a single daily dose. Children 2 to under 12 years of age: rectal enema dosage is 30 to 60 milliliters as a 25 to 30 percent weight/volume solution in a single daily dose. Children under 2 years of age: consult a doctor.

§ 334.56 Labeling of lubricant laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.14 includes the established name of the drug, if any, and identifies the product as a "lubricant laxative."

(b) *Indications—Other required statements.*

In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in 6 to 8 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in 2 to 15 minutes."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of products containing mineral oil identified in § 334.14(a) for oral use contains the following statements under the heading "Warnings."

(1) "Do not administer to children under 6 years of age, to pregnant women, to bedridden patients, or to persons with difficulty swallowing."

(2) "As with any drug, if you are nursing a baby, seek the advice of a health professional before using this product."

(3) "*Drug interaction precaution:* Do not take this product if you are presently taking a stool softener laxative."

(4) "Do not take with meals."

(5) The warnings in paragraph (c)(1) and (2) of this section supersede the general warning required in § 201.63.

(d) *Directions.* The labeling of products containing mineral oil identified in § 334.14 contains the following information under the heading "Directions."

(1) *Oral dosage.* Adults and children over 12 years of age: oral dosage is a minimum single dose of 15 milliliters to a maximum daily dose of 45 milliliters. Children 6 to under 12 years of age: oral dosage is a minimum single dose of 5 milliliters to a maximum daily dose of 15 milliliters. The dose may be taken as a single daily dose or in divided doses. Children under 6 years of age: consult a doctor.

(2) *Rectal enema dosage.* Adults and children over 12 years of age and over: rectal enema dosage is 120 milliliters in a single daily dose. Children 2 to under 12 years of age: rectal enema dosage is 60 milliliters in a single daily dose. Children under 2 years of age: consult a doctor.

§ 334.58 Labeling of saline laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.15 includes the established name of the drug, if any, and identifies the product as a "saline laxative."

(b) *Indications—Other required statements.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in ¼ to 6 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in 2 to 15 minutes."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statements under the heading "Warnings."

(1) *For products containing magnesium citrate identified in § 334.16(a) when formulated in oral solution.* "Store at temperatures between 46 and 86 °F (8 and 30 °C)."

(2) *For products containing phosphates identified in § 334.16 (d), (e), or (f).* (i) "Do not use this product if you have kidney disease unless directed by a doctor."

(ii) *Oral dosage forms.* "Do not give to children under 5 years of age unless directed by a doctor."

(iii) *Rectal dosage forms.* "Do not give to children under 2 years of age unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *Oral dosage forms.* "Drink a full glass (8 ounces) of liquid with each dose."

(2) *For products containing magnesium citrate identified in § 334.16(a).* Adults and children 12 years of age and over: oral dosage is 11 to 25 grams. Children 6 to under 12 years of age: oral dosage is 5.5 to 12.5 grams. Children 2 to under 6 years of age: oral dosage is 2.7 to 6.25 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(3) *For products containing magnesium hydroxide identified in § 334.16(b).* Adults and children 12 years of age and over: oral dosage is 2.4 to 4.8 grams. Children 6 to under 12 years of age: oral dosage is 1.2 to 2.4 grams. Children 2 to under 6 years of age: oral dosage is 0.4 to 1.2 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(4) *For products containing magnesium sulfate identified in § 334.16(c).* Adults and children 12 years of age and over: oral dosage is 10 to 30 grams. Children 6 to under 12 years of age: oral dosage is 5 to 10 grams. Children 2 to under 6 years of age: oral dosage is 2.5 to 5 grams. The dose may be taken as a single daily dose or in divided doses. Children under 2 years of age: consult a doctor.

(5) *For products containing sodium phosphate/sodium biphosphate identified in § 334.16(d) marketed as a solution*—(i) *Oral dosage.* Adults and children 12 years of age and over: oral dosage is sodium phosphate 3.42 to 7.56 grams, and sodium biphosphate 9.1 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is sodium phosphate 1.71 to 3.78 grams and sodium biphosphate 4.5 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is sodium phosphate 0.86 to 1.89 grams and sodium biphosphate 2.2 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor.

(ii) *Rectal enema dosage.* Adults and children 12 years of age and over: enema dosage is sodium phosphate 6.84 to 7.56 grams and sodium biphosphate 18.24 to 20.16 grams in a single daily dose. Children 2 to under 12 years of age: enema dosage is sodium phosphate 3.42 to 3.78 grams and sodium biphosphate 9.12 to 10.08 grams in a single daily dose. Children under 2 years of age: consult a doctor.

(6) *For products containing sodium phosphate identified in § 334.16(e).* Adults and children 12 years of age and over: oral dosage is 3.42 to 7.56 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is 1.71 to 3.78 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is 0.86 to 1.89 grams in a single daily dose. Children under 5 years of age: consult a doctor.

(7) *For products containing sodium biphosphate identified in § 334.16(f).* Adults and children 12 years of age and over: oral dosage is 4.5 to 20.2 grams in a single daily dose. Children 10 to under 12 years of age: oral dosage is 2.25 to 10.1 grams in a single daily dose. Children 5 to under 10 years of age: oral dosage is 1.12 to 5.05 grams in a single daily dose. Children under 5 years of age: consult a doctor.

§ 334.60 Labeling of stimulant laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.18 includes the established name of the drug, if any, and identifies the product as a "stimulant laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in 6 to 12 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in ¼ to 1 hour."

(3) *For products containing sennosides A and B in the dosage specified in § 334.60(d)(13).* The product should contain the following statement under the heading "Indications" instead of the statements required in §§ 334.50(a) and 334.60(b) (1) and (2): "For use as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for x-ray or endoscopic examination."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the labeling of the product contains the following statements under the heading "Warnings."

(1) *For products containing bisacodyl identified in § 334.18(b).* "Store at temperatures not above 86° F (30° C)."

(i) *Enteric-coated tablet dosage forms.* (*a*) "Do not chew tablets."

(*b*) "Do not give to children under 6 years of age, or to persons who cannot swallow without chewing, unless directed by a doctor."

(*c*) "Do not take this product within 1 hour after taking an antacid or milk."

(*d*) "This product may cause abdominal discomfort, faintness, and cramps."

(ii) *Rectal suppository dosage forms.* "This product may cause abdominal discomfort, faintness, rectal burning, and mild cramps."

(2) *For products containing phenolphthalein identified in § 334.18(g).* "If skin rash appears, do not use this product or any other preparation containing phenolphthalein."

(3) *For products containing sennosides A and B in the dosage specified in § 334.60(d)(13).* The product should contain the following statement under the heading "Warnings" instead of the statements required in § 334.50(b): "Do not use this product unless directed by a doctor."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing aloe identified in § 334.18(a).* Adults and children over 15 years of age: oral dosage is 120 to 250 milligrams in a single daily dose. Children 8 to under 15 years of age: oral dosage is 80 to 120 milligrams in a single daily dose. Children 6 to under 8 years of age: oral dosage is 40 to 80 milligrams in a single daily dose. Children under 6 years of age: consult a doctor.

(2) *For products containing bisacodyl identified in § 334.18(b)*—(i) *Oral dosage.* Adults and children 12 years of

age and over: oral dosage is 5 to 15 milligrams in a single daily dose. Children 6 to under 12 years of age: oral dosage is 5 milligrams in a single daily dose. Children under 6 years of age: consult a doctor.

(ii) *Rectal suppository dosage.* Adults and children 12 years of age and over: rectal suppository dosage is 10 milligrams in a single daily dose. Children 6 to under 12 years of age: rectal suppository dose is 5 milligrams in a single daily dose. Children under 6 years of age: consult a doctor.

(3) *For products containing casanthranol identified in § 334.18(c)(1).* Adults and children 12 years of age and over: oral dosage is 30 to 90 milligrams in a single daily dose. Children 2 to under 12 years of age: oral dosage is 15 to 45 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(4) *For products containing aromatic cascara fluidextract identified in § 334.18(c)(2)* Adults and children 12 years of age and over: oral dosage is 2 to 6 milliliters in a single daily dose. Children 2 to under 12 years of age: oral dosage is 1 to 3 milliliters in a single daily dose. Children under 2 years of age: consult a doctor.

(5) *For products containing cascara sagrada bark identified in § 334.18(c)(3).* Adults and children 12 years of age and over: oral dosage is 300 to 1000 milligrams in a single daily dose. Children 2 to under 12 years of age: oral dosage is 150 to 500 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(6) *For products containing cascara sagrada extract identified in § 334.18(c)(4).* Adults and children 12 years of age and over: oral dosage is 200 to 400 milligrams in a single daily dose. Children 2 to under 12 years of age: oral dosage is 100 to 200 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(7) *For products containing cascara sagrada fluidextract identified in § 334.18(c)(5).* Adults and children 12 years of age and over: oral dosage is 0.5 to 1.5 milliliters in a single daily dose. Children 2 to under 12 years of age: oral dosage is 0.25 to 0.75 milligrams in a single daily dose. Children under 2 years of age: consult a doctor.

(8) *For products containing castor oil identified in § 334.18(d).* Adults and children 12 years of age and over: oral dosage is 15 to 60 milliliters in a single daily dose. Children 2 to under 12 years of age: oral dosage is 5 to 15 milliliters in a single daily dose. Children under 2 years of age: consult a doctor.

(9) *For products containing danthron identified in § 334.18(e).* Adults and children 12 years of age and over: oral dosage is 75 to 150 milligrams in a single daily dose. Children under 12 years of age: consult a doctor.

(10) *For products containing dehydrocholic acid identified in § 334.18(f).* Adults and children 12 years of age and over: oral dosage is 250 to 500 milligrams three times a day, not to exceed 1500 milligrams in 24 hours. Children under 12 years of age: consult a doctor.

(11) *For products containing phenolphthalein identified in § 334.18(g).* Adults and children 12 years of age and over: oral dosage is 30 to 270 milligrams daily in a single or divided daily dose. Children 6 to under 12 years of age: oral dosage is 30 to 60 milligrams in a single or divided daily dose. Children 2 to under 6 years of age: oral dosage is 15 to 30 milligrams in a single or divided daily dose. Children under 2 years of age: consult a doctor.

(12) *For products containing sennosides A and B identified in § 334.18(h).*—(i) *Oral dosage.* Adults and children 12 years of age and over: oral dosage is 12 to 58 milligrams once or twice daily. Children 6 to under 12 years of age: oral dosage is 6 to 25 milligrams once or twice daily. Children 2 to under 6 years of age: oral dosage is 3 to 12.5 milligrams once or twice daily. Children under 2 years of age: consult a doctor.

(ii) *Rectal suppository dosage.* Adults and children 12 years of age and over: rectal suppository dosage is 30 milligrams once or twice daily. Children under 12 years of age: consult a doctor.

(13) *For products containing sennosides A and B identified in § 334.18(h) and labeled for use only as specified in paragraphs (b)(3) and (c)(3) of the section.* Adults and children 12 years of age and over: oral dosage is 160 milligrams in a single daily dose. Children under 12 years of age: consult a doctor.

§ 344.62 Labeling of stool softener laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.20 includes the established name of the drug, if any, and identifies the product as a "stool softener laxative."

(b) *Indications—Other required statements.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the following:

(1) *Oral dosage forms.* "This product generally produces bowel movement in 12 to 72 hours."

(2) *Rectal dosage forms.* "This product generally produces bowel movement in 2 to 15 minutes."

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

§ 334.64 Labeling of carbon dioxide-releasing laxative drug products.

(a) *Statement of identity.* The labeling of the product containing any ingredient identified in § 334.22 includes the established name of the drug, if any, and identifies the product as a "laxative."

(b) *Indications—Other required statement.* In addition to the indication identified in § 334.50(a), the product also contains a statement under the heading "Indications" that is limited to the phrase: "This product generally produces bowel movement in 5 to 30 minutes."

(c) *Warnings.* In addition to the warnings identified in § 334.50(b), the product also contains the following information under the heading "Warnings."

(1) "For rectal use only."

(2) "Do not lubricate with mineral oil or petrolatum prior to rectal insertion."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing the carbon dioxide-releasing ingredients identified in § 334.22(a).* Adults and children 12 years of age and over: rectal dosage is one suppository containing 1.2 to 1.5 grams of sodium biphosphate anhydrous, 0.04 to 0.05 gram of sodium acid pyrophosphate and 1 to 1.5 grams of sodium bicarbonate in a single daily dose. Children under 12 years of age: consult a doctor.

(2) *For products containing the carbon dioxide-releasing ingredients identified in § 334.22(b).* Adults and children 12 years of age and over: rectal dosage is one suppository containing 0.6 gram of sodium bicarbonate and 0.9 gram of potassium bitartrate in a single daily dose. Children under 12 years of age: consult a doctor.

(3) *For products containing the carbon dioxide-releasing ingredients identified in § 334.22(a) and (b).* "Moisten suppository by placing it under a water tap for 30 seconds or in a cup of water for at least 10 seconds before insertion."

§ 334.66 Labeling of bowel cleansing systems identified in § 334.32.

(a) *Statement of identity.* The labeling of the product containing the bowel cleansing systems identified in § 334.32(a), and (b) contains the established names of the drugs, if any,

and identifies the product as a "bowel cleansing system."

(b) *Indications.* The labeling of the product contains a statement of the indication under the heading "Indications" that is limited to the phrase: "For use as part of a bowel cleansing regimen in preparing patients for surgery or for preparing the colon for x-ray or endoscopic examination."

(c) *Warnings.* The labeling of the product contains the following statements instead of the warnings in § 334.50(b) under the heading "Warnings": "Do not use this product unless directed by a doctor."

(1) *For products containing the bowel cleansing system identified in § 334.32(a).* The labeling of the product also contains the warnings identified in §§ 334.50(b) (5), (6), (7), and (8); 334.58(c); and 334.60(c) as applicable.

(2) *For products containing the bowel cleansing system identified in § 334.32(b).* The labeling of the product also contains the warnings identified in §§ 334.50(b) (5), (6), (7), and (8); 334.58(c); 334.60(c); and 334.64(c) as applicable.

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) "Open and read the enclosed directions and labels at least 24 hours in advance of examination."

(2) "Follow each step and complete all instructions or the entire x-ray or endoscopic examination may have to be repeated."

(3) *Package insert.* The following information may be in the form of a package insert. (i) The manufacturer should include a detailed description of the diet to be followed as part of the bowel cleansing regimen, i.e., a clear liquid diet, together with a commentary on the importance of these dietary restrictions.

(ii) The manufacturer should include a detailed set of instructions for the intake of at least 40 ounces of clear fluid including black coffee, plain tea, strained fruit juice, soft drinks, or water, but not milk or cream, during the course of the bowel cleansing regimen. This shall include commentary on the importance of a high fluid intake to the success of the bowel cleansing regimen.

(iii) Detailed directions should be provided specifying the following dosages, time intervals, routes of administration, and sequence for the administration of the individual single entity laxative products included in the bowel cleansing system. This may specify exact times of day for administration of each laxative to insure proper time intervals and should be integrated with instructions regarding dietary restrictions and fluid intake to provide a detailed set of directions for the complete bowel cleansing regimen.

(*a*) *For the bowel cleansing system identified in § 334.32(a).* Twenty five grams magnesium citrate in oral solution; 15 to 20 milligrams bisacodyl administered orally 2 hours after administration of magnesium citrate in oral solution; 10 milligrams of bisacodyl administered by suppository 9 hours after the administration of the oral bisacodyl and at least 2 hours before the scheduled examination or x-ray.

(*b*) *For the bowel cleansing system identified in § 334.32(b).* Twenty five grams of magnesium citrate in oral solution; 270 milligrams phenolphthalein administered orally 2½ hours after administration of the magnesium citrate in oral solution; 1 carbon dioxide-releasing suppository of the type identified in § 334.22(b) administered 7 hours after administration of the phenolphthalein; 1 carbon dioxide-releasing suppository of the type identified in § 334.22(b) administered 8 hours after the first suppository and at least 2 hours before the scheduled examination or x-ray.

§ 334.80 Professional labeling.

The labeling of the product provided to health professionals (but not to the general public) contains the following information in addition to the labeling identified in §§ 334.50, 334.52, 334.54, 334.56, 334.58 and 334.60.

(a) *Indications.*—(1) *For products containing mineral oil identified in § 334.14.* "For preparing the colon for x-ray or endoscopic examination."

(2) *For products containing magnesium citrate in oral solution identified in § 334.16(a), sodium phosphate/sodium biphosphate identified in § 334.16(d), or bisacodyl identified in § 334.18(b).* "For use as part of a bowel cleansing regimen in preparing the patient for surgery or for preparing the colon for x-ray endoscopic examination."

(3) *For products containing castor oil identified in § 334.334.18(d).* "For preparing the colon for x-ray or endoscopic examination."

(4) *For products containing bisacodyl identified in § 334.18(b).* "For use as a laxative in postoperative care, antepartum care, postpartum care, and in preparation for delivery."

(b) *Warnings.* The labeling of the product contains the following information under the heading "Warnings."

(1) *For products containing karaya identified in § 334.10(c).* (i) "Rare cases of allergic reactions and urticaria caused by karaya have been reported."

(ii) "Inadequate fluid intake may cause obstructions of the large bowel."

(2) *For products containing sodium biphosphate or sodium phosphate identified in § 334.16 (d), (e), and (f).* "Do not use in patients with megacolon, as hypernatremic dehydration may occur. Use with caution in patients with impaired renal functions."

(3) *For products containing mineral oil identified in § 334.14.* "Side effects with the proper use of mineral oil are few. However, laxation, anal leakage, and dermatologic reactions may occur with chronic use and particularly with excess dosage. Owing to its property as a lipid solvent, mineral oil may interfere with the absorption of provitamin A, vitamin A, and vitamin D, leading to impairment of calcium and phosphorus metabolism. This occurs only under conditions of chronic usage. Administration of mineral oil may lower prothrombin levels, probably secondary to imparied vitamin K absorption, and regular use in pregnancy may predispose to hemorrhagic disease of the newborn. Because of possible interference with nutrition, mineral oil should not be ingested in close proximity to meals. These side effects occur very rarely and then only with chronic and abusive use."

(c) *Directions.* The labeling of the product may contain the following additional information under the heading "Directions."

(1) *For products containing malt soup extract identified in § 334.10(d).* Children under 2 years of age: oral dosage is 6 to 32 grams in a single daily dose.

(2) *For products containing polycarbophil identified in § 334.10(e).* Children under 2 years of age: oral dosage is 0.5 to 1 gram in a single daily dose.

(3) *For products containing glycerin identified in § 334.12(a).* Children under 2 years of age: (i) rectal suppository dosage is 1 to 1.7 grams of glycerin, in a single daily dose. (ii) rectal enema dosage is 2 to 5 milliliters of glycerin, as an 80 percent solution, in a single daily dose.

(4) *For products containing magnesium hydroxide identified in § 334.16(b).* Children under 2 years of age: oral dosage is 0.035 to 0.043 gram per kilogram per dose.

(5) *For products containing bisacodyl identified in § 334.18(b).* Children under 2 years of age: rectal suppository dosage is 5 milligrams in a single daily dose.

(6) *For products containing casanthranol identified in § 334.18(c)(1).*

Children under 2 years of age: oral dosage is 7.5 to 22.5 milligrams in a single daily dose.

(7) *For products containing aromatic cascara fluidextract identified in § 334.18(c)(2).* Children under 2 years of age: oral dosage is 0.5 to 1.5 milliliters in a single daily dose.

(8) *For products containing cascara sagrada bark identified in § 334.18(c)(3).* Children under 2 years of age: oral dosage is 75 to 250 milligrams in a single daily dose.

(9) *For products containing cascara sagrada extract identified in § 334.18(c)(4).* Children under 2 years of age: oral dosage is 50 to 200 milligrams in a single daily dose.

(10) *For products containing cascara sagrada fluidextract identified in § 334.18(c)(5).* Children under 2 years of age: oral dosage is 0.125 to 0.375 milligram in a single daily dose.

(11) *For products containing castor oil identified in § 334.18(d).* Children under 2 years of age: oral dosage is 1 to 5 milliliters in a single daily dose.

Interested persons may, on or before May 15, 1985, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. The agency has provided this 120-day period (instead of the normal 60 days) because of the number of OTC drug review documents being published concurrently. Written comments on the agency's economic impact determination may be submitted on or before May 15, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the Federal Register.

Interested persons, on or before January 15, 1986, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 17, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the Federal Register of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 17, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: December 31, 1984.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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